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(54) Title: NUCLEOSIDES FOR TREATMENT OF INFECTION BY CORONA VIRUSES, TOGA VIRUSES AND PICORNA VIRUSES

(57) Abstract: This invention is in the area of methods and pharmaceutical compositions for treating a host, especially a human, infected with a coronavirus, togavirus or picornavirus, comprising administering to that host an effective amount of a compound described herein or its salt, ester or prodrug. The compound can be administered alone or in combination with another optionally substituted pentofuranonucleoside or in combination with another anti-coronavirus, anti-togavirus and/or anti-picornavirus agent.

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NUCLEOSIDES FOR TREATMENT OF INFECTION BY CORONAVIRUSES, TOGAVIRUSES AND PICORNAVIRUSES

CROSS-REFERENCE FOR THE INVENTION

This application claims priority to U.S. Provisional No. 60/470,949, filed May 14, 2003.

FIELD OF THE INVENTION

This invention is in the area of methods and pharmaceutical compositions for the treatment of viral infections, including the viral causative agent of severe acute respiratory syndrome.

BACKGROUND OF THE INVENTION

Coronaviruses (order *Nidovirales*, family *Coronaviridae*, genus *Coronavirus*) are a diverse group of positively (+)-stranded RNA viruses that have been implicated in causing a variety of pathological conditions in both humans and other animals (Rota, et al., *Sciencexpress*, **May 1, 2003**, pp. 1-10). The coronavirus is composed of an envelope and helical nucleocapsid with club-shaped surface projections that provide "attachment to cells, hemagglutination, and membrane fusion." (Büchen-Osmond, C. (Ed), (2003). 00.026.0.01. *Coronaviridae*. In: *ICTVdB - The Universal Virus Database*, version 3. ICTVdB Management, The Earth Institute, Biosphere 2 Center, Columbia University, Oracle, AZ, USA). The complete genome is 25,000 to 33,000 nucleotides long and consists of a "single molecule of linear positive-sense single-stranded RNA (Büchen-Osmond, C. (Ed), (2003). 00.026.0.01. *Coronaviridae*. In: *ICTVdB - The Universal Virus Database*, version 3. ICTVdB Management, The Earth Institute, Biosphere 2 Center, Columbia University, Oracle, AZ, USA). The *Coronaviruses* are broken up into three

distinct categories based upon antigenic relationships whereby groups I and II are mammalian viruses and group III is an avian virus (Rota, et al., *Sciencexpress*, **May 1, 2003**, pp. 1-10). Within each antigenic category (I, II, or III), the Coronaviruses are further classified based upon their narrow host range and genome organization (Rota, et al., *Sciencexpress*, **May 1, 2003**, pp. 1-10). The mammalian viruses for **Antigenic group I** include human respiratory coronavirus (HCV-229E) (causes human respiratory infection), porcine transmissible gastroenteritis virus (TGEV) (causes pig respiratory infection, enteric infection, infectious peritonitis, immunological disorders, runting, nephritis, pancreatitis, parotitis, and adenitis), canine coronavirus (CCV) (causes dog enteric infection), feline enteric coronavirus (FECV) (causes cat enteric infection), feline infectious peritonitis virus (FIPV) (causes cat respiratory infection, enteric infection, hepatitis, neurologic infection, infectious peritonitis, immunological disorders, runting, nephritis, pancreatitis, parotitis, and adenitis), and rabbit coronavirus (RbCV) (causes rabbit , infectious peritonitis, immunological disorders, runting, nephritis, pancreatitis, parotitis, and adenitis) (K.V. Holmes and M.M.C. Lai, "*Coronaviridae*: The viruses and their replication," *Fields Virology,* B.N. Fields, D.M. Knipe and P.M. Howley, Editiors; 1996, Lippincott-Raven Publishers, Philadelphia, PA; Chpt. 34, pp. 1075-93).

The mammalian viruses for **Antigenic group II** include human respiratory coronavirus (HCV-OC43) (causes human respiratory infection and may be implicated in enteric infections), mouse hepatitis virus (MHV) (causes mouse respiratory infection, enteric infection, hepatitis, and neurologic infection), sialodacryoadnavirus (SDAV) (causes rat neurologic infection), porcine hemagglutinating encephalomyelitis virus (HEV) (causes pig respiratory infection, enteric infection, and neurologic infection), bovine coronavirus (BCV) (causes cow enteric infection), rabbit enitis coronavirus (RbEVC) (causes rabbit enteric infection), and turkey coronavirus (TCV) (causes turkey respiratory infection, enteric infection, infectious peritonitis, immunological disorders, runting, nephritis, pancreatitis, parotitis, and adenitis) (K.V. Holmes and M.M.C. Lai, "*Coronaviridae*: The viruses and their replication," *Fields Virology,* B.N. Fields, D.M. Knipe and P.M. Howley, Editiors; 1996, Lippincott-Raven Publishers, Philadelphia, PA; Chpt. 34, pp. 1075-93).

The avian virus for **Antigenic group III** include avian infectious bronchitis virus (IBV) (causes chicken respiratory infection, hepatitis, infectious peritonitis,

immunological disorders, runting, nephritis, pancreatitis, parotitis, and adenitis) (K.V. Holmes and M.M.C. Lai, "*Coronaviridae*: The viruses and their replication," *Fields Virology,* B.N. Fields, D.M. Knipe and P.M. Howley, Editiors; 1996, Lippincott-Raven Publishers, Philadelphia, PA; Chpt. 34, pp. 1075-93).

The *Togaviridae* family of viruses are separated into two genera: the alphaviruses and the rubiviruses (Büchen-Osmond, C. (Ed), (2003). 00.026.0.01. *Togaviridae*. In: *ICTVdB - The Universal Virus Database*, version 3. ICTVdB Management, The Earth Institute, Biosphere 2 Center, Columbia University, Oracle, AZ, USA). The complete genome of this family of viruses is composed of 9,700 to 11,800 nucleotides and contains "one molecule of linear positive-sense single stranded RNA." This family of viruses infects both vertebrates and plants.

The complete genome of the alphavirus genus of the *Togaviridae* family is 11,000 to 12,000 nucleotides and is composed of "one molecule of linear positive-sense single stranded RNA (Büchen-Osmond, C. (Ed), (2003). 00.026.0.01. *Alphavirus*. In: *ICTVdB - The Universal Virus Database*, version 3. ICTVdB Management, The Earth Institute, Biosphere 2 Center, Columbia University, Oracle, AZ, USA). The alphaviruses, unlike the coronaviruses discussed above, have a broad host range and have the ability to replicate in a variety of cell types (S. Schlesinger and M.J. Schlesinger, "*Togaviridae*: The viruses and their replication," *Fields Virology,* B.N. Fields, D.M. Knipe and P.M. Howley, Editiors; 1996, Lippincott-Raven Publishers, Philadelphia, PA; Chpt. 27, pp. 825-41).

Among the viruses classified within this genus are the Sindbis virus, Eastern/Western encephalitis viruses, Semliki Forest virus, and Ross River virus. The genus *Rubivirus* of the *Togaviridae* family are distinguished from alphaviruses on the basis of a limited host range. This genus consists of only the Rubella virus, which is found exclusively in humans.

The *Picornaviridae* family of viruses are categorized as small, naked, icosahedral, RNA-containing animal viruses that are separated into six genera: the rhinoviruses, enteroviruses, aphthoviruses, cardioviruses, hepatoviruses, and unassigned (R.R. Rueckert, "*Picornaviridae*: The viruses and their replication," *Fields Virology,*

B.N. Fields, D.M. Knipe and P.M. Howley, Editiors; 1996, Lippincott-Raven Publishers, Philadelphia, PA; Chpt. 21, pp. 609-54).

The genus rhinovirus includes the human rhinoviruses 1A-100, 1B, "Hanks," and bovine rhinoviruses 1, 2, and 3. The human rhinoviruses consist of at least 105 serotypes (a classification scheme based on the variation of surface epitopes) and represent the most common etiological agent for the common cold. This is a major point of economic concern as it results in lost work days for everyone and "predisposes [the young and elderly] to secondary bacterial infections - a major problem in infants and elderly. (retrieved from *All the Virology on the World Wide Web*, Internet URL: http://www.tulane.edu/dmsander/WWW/335/Picornaviruses.html)."

The genus enterovirus, which inhabits the enteric track, is composed of a total of 95 serotypes. These serotypes include the Human polioviruses 1, 2, and 3 (A23-echovirus; echo = Enteric Cytopathic Human Orphan viruses) (3 serotypes), Human coxsackieviruses A1-22, 24 (23 serotypes), Human coxsackieviruses B1-6 (swine vesicular disease virus is very similar to coxsackie B5 virus) (6 serotypes), Human echoviruses 1-7, 9, 11-27, 29-34 (30 serotypes; these viruses show a seasonal, epidemic pattern of infection primarily associated with meningitis, paralysis (usually less severe than acute poliomyelitis), and myocarditis), Human enteroviruses 68-71 (4 serotypes), Vilyuisk virus (1 serotype), Simian enteroviruses 1-18 (18 serotypes), Bovine enteroviruses 1, 2 (2 serotypes), and Porcine enteroviruses 1-8 (8 serotypes) (R.R. Rueckert, "*Picornaviridae*: The viruses and their replication," *Fields Virology*, B.N. Fields, D.M. Knipe and P.M. Howley, Editiors; 1996, Lippincott-Raven Publishers, Philadelphia, PA; Chpt. 21, pp. 609-54).

The genus apthovirus "infect[s] cloven-footed animals [with foot-and-mouth disease virus (FMDV)], especially cattle, goats, pigs, and sheep," while rarely infecting humans. The apthoviruses, therefore, have the potential to impose significant worldwide economic burdens when substantial numbers of cattle become infected. Further, this particular genus is highly labile and the complete genome consists of 100-170 nucleotides (retrieved from *All the Virology on the World Wide Web*, Internet URL: http://www.tulane.edu/dmsander/WWW/335/Picornaviruses.html). While seven serotypes have been identified to date (A; C; O; SAT1,2,3; Asia-1), at least fifty-three subtypes have also been characterized.

The cardioviruses consist of two serotypes. Namely, Encephalomyocarditis (EMC) virus (a mouse virus that can infect humans, elephants, and squirrels; includes mengovirus, Maus-Elberfield virus, and the Columbia virus) and Theiler's murine encephalocyelitis (TME) virus (TO, GDVII) (R.R. Rueckert, "*Picornaviridae*: The viruses and their replication," *Fields Virology,* B.N. Fields, D.M. Knipe and P.M. Howley, Editiors; 1996, Lippincott-Raven Publishers, Philadelphia, PA; Chpt. 21, pp. 609-54). of EMCV (really a mouse virus, but can infect man, elephants, and squirrels).

The last two genera of the *Picornaviridae* family are the Hepatovirus and the Unassigned. The Hepatovirus (1 serotype) has Human hepatitis virus A' as its sole member and the Unassigned genus (3 serotypes) includes the Equine rhinoviruses 1,2, cricket paralysis virus, and the Drosophila C virus.

New to the mammalian coronavirus groups is the coronavirus causative agent of severe acute respiratory syndrome (SARS), a disease that threatens to become a global epidemic. Easily transmissible and capable of killing 4-15% of the people who contract it, SARS has spread rapidly from its place of origin in Guangdong Province, China, to most of the rest of the world; only Europe and South America are relatively unaffected by this disease, which is spread by travelers. It is believed to have begun in mid-November, 2002, although it was not recognized until late February, 2003 (Jane Parry, *British Medical J.,* **April 19, 2003,** *326*:839; Editorial Comment, *British Medical J.,* **April 19, 2003,** *326*:831-2). As of May 5, 2003, more than 6,000 patients from 29 countries have been diagnosed with the disease (C. Drosten and W. Preiser, *Kamps-Hoffmann SARS Reference – 05/2003*, **May 12, 2003**, retrieved from Bernd Sebastian Kamp, Internet URL: http://www.amedeo.com/sars/sars.htm).

SARS is characterized by a non-specific onset and an incubation period of 2-10 days, both of which favor transmission among individuals. Transmission appears to occur by close contacts with infected individuals, thus suggesting that spread is via body secretions and fluids, but may also occur by droplets via aerosol routes. Usually the disease begins with a prodrome of fever greater than 38 °C., sometimes accompanied by chills, headaches, malaise and/or myalgias. Respiratory symptoms generally are mild at this early stage. However, at about day 3 to day 4, a dry cough or dyspnea, sore throat, and erythema on the trunk of the patient appear. These symptoms are accompanied by hypoxemia that may require mechanical intervention and bilateral chest opacifications.

While the chests of some patients remain clear, most patients exhibit foci of interstitial infiltrates that eventually become generalized, opaque patches or "crackles". Chest radiographs from some late stage SARS patients show areas of foci consolidation (*Canada Communicable Disease Report, PREVIEW,* 21 March 2003). Results of laboratory tests indicate elevated levels of aspartate aminotransferase, lactate dehydrogenase, and maximal levels of C-reactive protein at about day 7 or day 8, together with lymphopenia, leukopenia, and thrombocytopenia. A period of convalescence generally begins on about day 10 following infection except in about 4-15% of the infected population in which the disease is fatal (Drosten et al., *The New England Journal of Medicine Online*, April 10, 2003, pp. 1-10).

The etiologic agent responsible for SARS is a new coronavirus, SARS Co-V, first suggested by J. Peiris, C. Drosten, and T.G. Ksiazek working at three different research facilities. M. Peiris and his research group in Canada were first to successfully sequence the SARS Co-V genome, which was later confirmed by the Centers for Disease Control. They identified 11 open reading frames (ORFs) that correspond to regions predicted to encode a variety of polypeptides including polymerase proteins (polymerase 1a and 1b), spike protein (S), small membrane protein (E), membrane protein (M), and nucleocapsid protein (N). The complete SARS Co-V genome comprises 29,727 nucleotides and has a structural organization that is similar to other coronaviruses. (Retrieved from the *Center for Disease Control*; Internet URL: http://www.cdc.gov/ncidod/sars/sequence.html). Moreover, a recent article by Rota, et al., however, lends further support that the SARS Co-V is phylogenetically distinct from any previously classified coronavirus and suggested that these unique genomic features may give rise to its infectious role in SARS (Rota, et al., *Sciencexpress*, **May 1, 2003**, pp. 1-10).

Preliminary studies show that SARS Co-V is stable in feces and urine at room temperature for 1-2 days, and appears to have greater stability in higher pH stools from patients with diarrhea. Supernatants of infected cells cultures show a minimal reduction in SARS Co-V concentration after 21 days at 4 °C. and –80 °C. A viral reduction of one log is observed after 48 hours at room temperature, indicating that this coronavirus is more stable than other known human coronaviruses. Inactivation of SARS Co-V is accomplished by heating to 56 °C., and infectivity is lost with exposure to certain fixatives and disinfectants (C. Drosten and W. Preiser, *Kamps-Hoffmann SARS*

Reference – 05/2003, May 12, 2003, retrieved from Bernd Sebastian Kamp, Internet URL: http://www.amedeo.com/sars/sars.htm).

To date, treatment of patients infected with SARS Co-V consists of administering Ribavirin, a broad spectrum anti-RNA-viral agent, however it is not very efficacious. Efforts also are underway to produce an anti-SARS vaccine, but this is expected to take 1-2 years to develop. Thus, there is an urgent need to find ways to treat patients with SARS before a vaccine is available that can result in prevention of the disease.

Examples of antiviral agents that have been identified as active against (+)-RNA viruses include interferon and ribavirin (Battaglia, A.M. *et al.*, *Ann. Pharmacother*, 2000,. *34*, 487-494); Berenguer, M. *et al. Antivir. Ther.*, 1998, *3* (Suppl. 3), 125-136).

Interferon

Interferons (IFNs) are glycoproteins produced by immune cells in response to viral infection. IFNs inhibit viral replication of many viruses, and are known to suppress serum viral RNA to undetectable levels. Additionally, IFN normalizes serum amino transferase levels. Unfortunately, the effects of IFN are temporary and a sustained response occurs in only 8%-9% of patients with chronic viral infection (Gary L. Davis. *Gastroenterology* 118:S104-S114, 2000).

Interferons (IFNs) have been commercially available for the treatment of chronic hepatitis for nearly a decade. In addition, a number of patents disclose anti-viral treatments using interferon-based therapies. For example, U.S. Patent No. 5,928,636 to Alber *et al.* discloses the combination therapy of interleukin-12 and interferon alpha for the treatment of infectious diseases. U.S. Patent No. 5,908,621 to Glue *et al.* discloses the use of polyethylene glycol modified interferon for the treatment of viral infections. U.S. Patent No. 5,849,696 to Chretien *et al.* discloses the use of thymosins, alone or in combination with interferon, for treating viral infections. U.S. Patent No. 5,830,455 to Valtuena *et al.* discloses a combination anti-viral therapy employing interferon and a free radical scavenger. U.S. Patent No. 5,738,845 to Imakawa discloses the use of human interferon tau proteins for treating viral infections. Other interferon-based treatments are disclosed in U.S. Patent No. 5,676,942 to Testa *et al.*, U.S. Patent No. 5,372,808 to Blatt *et al.*, and U.S. Patent No. 5,849,696.

Ribavirin (1-β-D-ribofuranosyl-1-1,2,4-triazole-3-carboxamide) is a synthetic, non-interferon-inducing, broad spectrum antiviral nucleoside analog. It is sold under the trade names Virazole™ (The Merck Index, 11th edition, Editor: Budavari, S., Merck & Co., Inc., Rahway, NJ, p1304, 1989); Rebetol (Schering Plough) and Co-Pegasus (Roche). United States Patent No. 3,798,209 and RE29,835 (ICN Pharmaceuticals) disclose and claim ribavirin. Ribavirin is structurally similar to guanosine, and has in vitro activity against several DNA and RNA viruses (Gary L. Davis. *Gastroenterology* **2000**, 118:S104-S114). U.S. Patent No 4,211,771 (to ICN Pharmaceuticals) discloses the use of ribavirin as an antiviral agent. *Ribavirin* (Battaglia, A.M. et al., Ann. Pharmacother, 2000,. 34, 487-494; Berenguer, M. et al. Antivir. Ther., 1998, 3 (Suppl. 3), 125-136).

Ribavirin reduces serum amino transferase levels to normal in 40% of patients, but it does not lower viral serum levels (Gary L. Davis. *Gastroenterology* **2000**, 118:S104-S114). Thus, ribavirin alone is not effective in reducing viral RNA levels. Additionally, ribavirin has significant toxicity and is known to induce anemia.

Combination of Interferon and Ribavirin

Schering-Plough sells ribavirin as Rebetol® capsules (200 mg). The U.S. FDA has approved Rebetol capsules to treat chronic viral infection in combination with Schering's alpha interferon-2b products Intron® A and PEG-Intron™. Rebetol capsules are *not* approved for monotherapy (*i.e.*, administration independent of Intron®A or PEG-Intron™), although Intron®A and PEG-Intron™ are approved for monotherapy (*i.e.*, administration without ribavirin). Hoffman La Roche is selling ribavirin under the name CoPegus in Europe and the United States, also for use in combination with interferon for the treatment of viral infection. Other alpha interferon products include Roferon-A (Hoffmann-La Roche), Infergen® (Intermune, formerly Amgen's product), and Wellferon® (Wellcome Foundation).

The combination of IFN and ribavirin for the treatment of viral infection has been reported to be effective in the treatment of IFN naïve patients (Battaglia, A.M. *et al.*, *Ann. Pharmacother.* 34:487-494, 2000). However, the side effects of combination

therapy can be significant and include hemolysis, flu-like symptoms, anemia, and fatigue (Gary L. Davis. *Gastroenterology* 118:S104-S114, 2000).

Other examples of antiviral agents that have been identified as active against certain (+)-RNA viruses are:

(1) Substrate-based NS3 protease inhibitors (for example, Attwood *et al.*, *Antiviral peptide derivatives*, PCT WO 98/22496, **1998**; Attwood *et al.*, *Antiviral Chemistry and Chemotherapy* **1999**, *10*, 259-273; Attwood *et al., Preparation and use of amino acid derivatives as anti-viral agents,* German Patent Pub. DE 19914474; Tung *et al. Inhibitors of serine proteases,* PCT WO 98/17679), including alphaketoamides and hydrazinoureas, and inhibitors that terminate in an electrophile such as a boronic acid or phosphonate (for example, Llinas-Brunet et al, PCT WO 99/07734);

(2) Non-substrate-based inhibitors such as 2,4,6-trihydroxy-3-nitro-benzamide derivatives (for example, Sudo K. *et al.*, *Biochemical and Biophysical Research Communications*, **1997**, *238*, 643-647; Sudo K. *et al. Antiviral Chemistry and Chemotherapy*, **1998**, *9*, 186), including RD3-4082 and RD3-4078, the former substituted on the amide with a 14 carbon chain and the latter processing a *para*-phenoxyphenyl group;

(3) Thiazolidine derivatives that show relevant inhibition in a reverse-phase HPLC assay (for example, Sudo K. *et al., Antiviral Research*, **1996**, *32*, 9-18), especially compound RD-1-6250, possessing a fused cinnamoyl moiety substituted with a long alkyl chain, RD4 6205 and RD4 6193;

(4) Thiazolidines and benzanilides for example, identified in Kakiuchi N. *et al. J. EBS Letters 421*, 217-220; Takeshita N. *et al. Analytical Biochemistry*, **1997**, *247*, 242-246;

(5) A phenanthrenequinone possessing activity against protease in a SDS-PAGE and autoradiography assay isolated from the fermentation culture broth of *Streptomyces* sp., for example, Sch 68631 (for example, Chu M. *et al., Tetrahedron Letters*, **1996**, *37*, 7229-7232), and Sch 351633, isolated from the fungus *Penicillium griscofuluum,* which

demonstrates activity in a scintillation proximity assay (for example, Chu M. *et al.*, *Bioorganic and Medicinal Chemistry Letters 9*, 1949-1952);

(6) Selective NS3 inhibitors based on the macromolecule elgin c, isolated from leech (for example, Qasim M.A. *et al.*, *Biochemistry*, **1997**, *36*, 1598-1607);

(7) Polymerase inhibitors such as nucleotide analogues, gliotoxin (for example, Ferrari R. *et al. Journal of Virology*, **1999**, *73*, 1649-1654), and the natural product cerulenin (for example, Lohmann V. *et al.*, *Virology*, **1998**, *249*, 108-118);

(8) Antisense phosphorothioate oligodeoxynucleotides (S-ODN) complementary to sequence stretches in the 5' non-coding region (NCR) of the virus (for example, Alt M. *et al.*, *Hepatology*, **1995**, *22*, 707-717);

(9) Inhibitors of IRES-dependent translation (for example, Ikeda N *et al.*, *Agent for the prevention and treatment of hepatitis C,* Japanese Patent Pub. JP-08268890; Kai Y. *et al. Prevention and treatment of viral diseases*, Japanese Patent Pub. JP-10101591);

(10) Nuclease-resistant ribozymes (for example, Maccjak, D. J. *et al.*, *Hepatology* **1999**, *30*, abstract 995);

(11) Nucleoside analogs have also been developed for the treatment of viral infections;

(12) Other miscellaneous compounds including 1-amino-alkylcyclohexanes (for example, U.S. Patent No. 6,034,134 to Gold *et al.*), alkyl lipids (for example, U.S. Pat. No. 5,922,757 to Chojkier *et al.*), vitamin E and other antioxidants (for example, U.S. Pat. No. 5,922,757 to Chojkier *et al.*), squalene, amantadine, bile acids (for example, U.S. Pat. No. 5,846,964 to Ozeki *et al.*), N-(phosphonoacetyl)-L-aspartic acid (for example, U.S. Pat. No. 5,830,905 to Diana *et al.*), benzenedicarboxamides (for example, U.S. Pat. No. 5,633,388 to Diana *et al.*), polyadenylic acid derivatives (for example, U.S. Pat. No. 5,496,546 to Wang *et al.*), 2',3'-dideoxyinosine (for example, U.S. Pat. No. 5,026,687 to Yarchoan *et al.*), and benzimidazoles (for example, U.S. Pat. No. 5,891,874 to Colacino *et al.*); and

(13) Other compounds currently in clinical development for treatment of a coronavirus, togavirus, and/or picornavirus infection, or more generally any (+)-RNA active agent.

Idenix Pharmaceuticals, Ltd. discloses branched nucleosides, and their use in the treatment of HCV and flaviviruses and pestiviruses in US Patent Publication No. 2003/0050229 A1 and US Patent Publication No. 2003/0060400 A1, which correspond to International Publication Nos. WO 01/90121 and WO 01/92282. A method for the treatment of hepatitis C infection (and flaviviruses and pestiviruses) in humans and other host animals is disclosed in the Idenix publications that includes administering an effective amount of a biologically active 1', 2', 3' or 4'-branched β-D or β-L nucleosides or a pharmaceutically acceptable salt or prodrug thereof, administered either alone or in combination, optionally in a pharmaceutically acceptable carrier. See also U.S. Patent Publication Nos. 2004/0006002 and 2004/0006007 as well as WO 03/026589 and WO 03/026675. Idenix Pharmaceuticals, Ltd. also discloses in US Patent Publication No. 2004/0077587 pharmaceutically acceptable branched nucleoside prodrugs, and their use in the treatment of HCV and flaviviruses and pestiviruses in prodrugs. See also PCT Publication Nos. WO 04/002422, WO 04/002999, and WO 04/003000.

ICN Pharmaceuticals, Inc. discloses various nucleoside analogs that are useful in modulating immune response in US Patent Nos. 6,495,677 and 6,573,248. See also WO 98/16184, WO 01/68663, and WO 02/03997.

US Patent Publication Nos. 2003/083307 A1 and US 2003/008841 A1, and the corresponding International Patent Publication Nos. WO 02/18404 (PCT/EP01/09633; published August 21, 2001); WO 02/100415 and WO 02/094289, filed by F. Hoffmann-La Roche AG discloses various nucleoside analogs for the treatment of HCV RNA replication.

Pharmasset Limited discloses various nucleosides and antimetabolites for the treatment of a variety of viruses, in WO 02/32920, WO 01/79246, WO 02/48165, WO 03/068162, WO 03/068164 and 2004/013298.

Merck & Co., Inc. and Isis Pharmaceuticals disclose in US Patent Publication No. 2002/0147160 and the corresponding International Patent Publication Nos. WO 02/057425 (PCT/US02/01531; filed January 18, 2002) and WO 02/057287 (PCT/US02/03086; filed January 18, 2002) various nucleosides, and in particular several pyrrolopyrimidine nucleosides, for the treatment of viruses whose replication is

dependent upon RNA-dependent RNA polymerase. See also WO 03/068244, WO 04/003138, WO 04/007512, and WO 04/009020.

US Patent Publication No. 2003/028013 A1 as well as International Patent Publication Nos. WO 03/051899, WO 03/061576, WO 03/062255 WO 03/062256, WO 03/062257, and WO 03/061385, filed by Ribapharm, also are directed to the use of certain nucleoside analogs to treat viral infections.

In view of the severity of diseases associated with coronaviruses, togaviruses, and picornaviruses and their pervasiveness in animals and humans, it is an object of the present invention to provide a compound, method and composition for the treatment of a host infected with any one of these (+)-stranded RNA viruses.

It is yet another object of the present invention to provide a compound, composition, and method of use for the treatment of a host, especially a human, infected with the SARS coronavirus in an attempt to halt the spread of SARS.

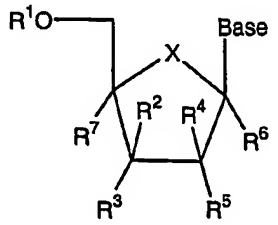
It is another object of the present invention to provide a method and pharmaceutically-acceptable composition for the prophylaxis and treatment of a host, and particularly a human, infected with a togavirus, picornavirus and/or a coronavirus, and SARS-CoV in particular.

It is still another object of the invention to provide compounds and physiologically acceptable salts, esters or prodrugs thereof, for the manufacture of a medicament to be used in the prophylaxis or treatment of a host infected with a togavirus, picornavirus and/or a coronavirus, and especially SARS-CoV.

SUMMARY OF THE INVENTION

Methods and compositions for the treatment of infections caused by a coronavirus, togavirus or picornavirus are described that include administering an effective amount of a β-D or β-L-nucleoside of the formula below or a pharmaceutically acceptable salt or prodrug thereof.

In a first principal embodiment, the use of a compound for the treatment of a coronavirus, togavirus or picornavirus is provided wherein the compound is of the formula (AA), or a pharmaceutically acceptable salt or prodrug thereof:



AA

or a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, wherein:

R^1 is H, phosphate or phosphonate (including mono-, di-, or triphosphate or a stabilized phosphate prodrug); optionally substituted acyl (including lower acyl); optionally substituted alkyl (including lower alkyl); optionally substituted sulfonate ester including alkyl or arylalkyl sulfonyl such as methanesulfonyl; optionally substituted aryl; optionally substituted benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of an aryl given herein; optionally substituted arylsulfonyl; a lipid, including a phospholipid; an amino acid derivative; a carbohydrate; a peptide; cholesterol; or a pharmaceutically acceptable leaving group that when administered *in vivo*, provides a compound wherein R^1 is independently H or phosphate;

each R^2 and R^4 independently is H, OH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, halo (F, Cl, Br, or I), NO_2, NH_2, N_3, CH_2N_3, CH_2NH_2, CN, CH_2CN, CH_2N_3, CH_2NHCH_3, $CH_2N(CH_3)_2$, CH_2OH, halogenated alkyl, alkoxy, CF_3, $C(A)_3$, 2-Br-ethyl, CH_2F, CH_2Cl, CH_2CF_3, CF_2CF_3, $CH_2(A)$, $C(A)_2C(A)_3$, SCN, OCN, NCO, haloalkenyl, Br-vinyl, haloalkynyl; $-(CH_2)_mC(O)OR^{13}$, $-(CH_2)_mC(O)SR^{13}$; -O(alkenyl), $-(CH_2)_mNHR^{13}$, $-(CH_2)_mN(R^{13})_2$, $-(CH_2)_mC(O)NHR^{13}$, $-(CH_2)_mC(O)N(R^{13})_2$, $-C(O)OR^{13}$, $-O(R^{13})$, an optionally substituted carbocycle, an optionally substituted heterocycle, an

optionally substituted heteroaryl (preferably a heteroaromatic ring having one or more O, S and/or N atoms), or C_{3-7} cycloalkylamino;

each R^3, R^5 and R^6 independently is H, OH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, halo (F, Cl, Br, or I), NO_2, NH_2, N_3, CH_2N_3, CH_2NH_2, CN, CH_2CN, CH_2N_3, CH_2NHCH_3, $CH_2N(CH_3)_2$, CH_2OH, halogenated alkyl, alkoxy, CF_3, $C(A)_3$, 2-Br-ethyl, CH_2F, CH_2Cl, CH_2CF_3, CF_2CF_3, $CH_2(A)$, $C(A)_2C(A)_3$, SCN, OCN, NCO, haloalkenyl, Br-vinyl, haloalkynyl; $-(CH_2)_mC(O)OR^{13}$, $-(CH_2)_mC(O)SR^{13}$; -O(alkenyl), $-(CH_2)_mNHR^{13}$, $-(CH_2)_mN(R^{13})_2$, $-(CH_2)_mC(O)NHR^{13}$, $-(CH_2)_mC(O)N(R^{13})_2$, $-C(O)OR^{13}$, $-O(R^{13})$, an optionally substituted carbocycle (preferably a 3-7 membered carbocyclic ring such as, for example, a C_{3-7} cycloalkylamino), an optionally substituted heterocycle (preferably a 3-7 membered heterocyclic ring having one or more O, S and/or N), an optionally substituted heteroaryl (preferably a heteroaromatic ring having one or more O, S and/or N atoms), a C_{3-7} cycloalkylamino, CF_3, mercapto, optionally substituted C_{1-4} alkyl, C_{1-12} alkoxy, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{2-6} alkenyloxy, C_{1-4} alkylthio, C_{1-8} alkylcarbonyloxy, aryloxycarbonyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, Br-vinyl, -C(O)O(alkyl), O-phosphate or O-phosphonate (including mono-, di-, or triphosphate or a stabilized phosphate prodrug); O-acyl (including lower acyl); O-alkyl (including lower alkyl); O-sulfonate ester including O-alkyl or O-arylalkyl sulfonyl including O-methanesulfonyl; O-aryl; O-benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of an aryl given herein; -OC(O)O-aryl; -OC(O)O-aralkyl; -S(acyl); -S(alkyl); -S(alkenyl); optionally substituted O-arylsulfonyl; an O-linked lipid, including an O-phospholipid; an O-linked amino acid; an O-linked carbohydrate; an O-linked peptide; O-linked cholesterol; or other O-linked pharmaceutically acceptable leaving group that when administered *in vivo*, provides independently OH or O-phosphate;

each R^7 is independently H, $-OR^1$, -OH, $-NO_2$, $-CF_3$, $-NH_2$, Cl, F, Br, I, N_3, CN, optionally substituted alkyl, optionally substituted alkenyl or alkynyl, Br-vinyl, $-CH_2OH$, -O(R), alkoxy, $-(CH_2)_mC(O)O(R)$, -OC(O)O-aryl, -OC(O)O-aralkyl, -SR, $-(CH_2)_mNHR$, $-(CH_2)_mN(R)_2$, or C_{3-7} cycloalkylamino;

each R is H, alkyl, alkenyl, alkynyl, acyl, aryl or aralkyl;

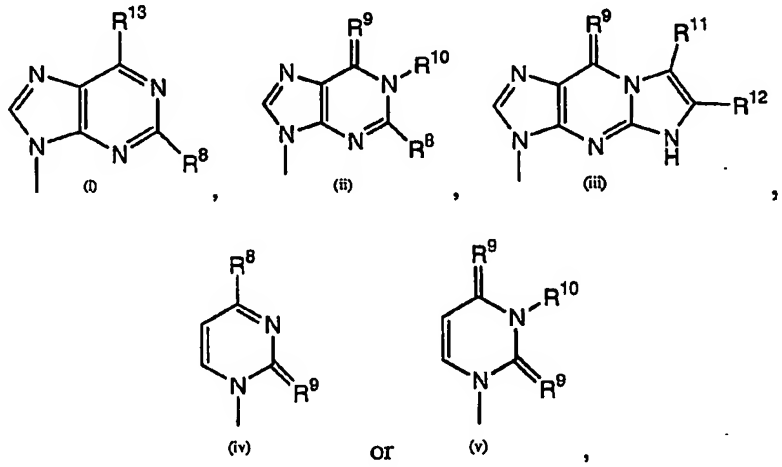
X is O, S, SO_2, CH_2, or CHOH;

m is 0, 1 or 2;

R^{13} is H, alkyl, alkenyl, alkynyl, acyl, aryl or aralkyl;

A is H, OH, C_{1-4} alkyl, halo (F, Cl, Br, or I), azido, cyano, C_{2-6} alkenyl, C_{2-6} alkynyl, Br-vinyl, 2-Br-ethyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), CF_3, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, or -N(acyl)$_2$; and

Base is as defined in the specification, including a purine or pyrimidine or a compound including but not limited to:



wherein:

each R^8, R^{10}, R^{11}, R^{12} and R^{13} independently is H, NH_2, SH, CF_3, halo, NO_2, N_3, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl (preferably optionally substituted phenyl), -NH-cycloalkyl, -NH-cycloalkenyl, -NH-heterocycle, -NH-heteroaryl, -O-cycloalkyl, -O-cycloalkenyl, -O-heterocycle, -O-heteroaryl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{3-6} cycloalkylamino, C_{1-4} alkyl-C(=O)OH, C_{1-4} alkyl-C(=O)O-aryl (preferably C_{1-4} alkyl-C(=O)O-phenyl), C_{1-4} alkyl-C(=O)O-heterocycle, C_{1-4} alkyl-C(=O)O-heteroaryl, or C_{1-4} alkoxy; and

R^9 is O or S;

and all tautomeric, enantiomeric and stereoisomeric forms thereof.

In a particular embodiment of the invention, the compound for use in the present invention is in the form of its 2', 3', and/or 5'-prodrug. In one embodiment, the compound is a prodrug that includes biologically cleavable moieties at the 2', 3' and/or 5' positions. In one embodiment, the compound is an acyl prodrug with biologically cleavable acyl moieties at the 2', 3' and/or 5' positions. In a particular embodiment, the compound is an amino acid ester prodrug with biologically cleavable amino acid moieties at the 2', 3' and/or 5' positions. Preferred moieties are amino acid esters including valyl, and alkyl esters including acetyl. Therefore, this invention specifically includes the 2'-L-amino acid ester, 3'-L-amino acid ester, 2',5'-L-diamino acid ester, and 3',5'-L-diamino acid ester of the nucleosides of the present invention; and the 2'-ester, 3'-ester, 2',5'-diester and 3',5'-diester of the nucleosides wherein (i) the 2' and/or 3' ester is an amino acid ester and the 5'-ester is an alkyl or aryl ester; (ii) both esters are amino acid esters; (iii) both esters are independently alkyl or aryl esters; and (iv) the 2' and/or 3' ester is independently an alkyl or aryl ester and the 5'-ester is an amino acid ester.

In one embodiment, the active compounds of the present invention can be administered in combination, alternation or sequential steps with another antiviral agent, including an anti-(+)-stranded RNA virus agent. In preferred embodiments, an anti-(+)-stranded RNA virus compound is used that exhibits an EC_{50} of less than 10 μM, and preferably less than 1-5 μM.

It is intended that the active compounds of the present invention include both β-D and β-L nucleoside compounds of the general formula (AA) or a pharmaceutically acceptable salt or prodrug thereof; a pharmaceutical composition comprising one or more of these compounds; a medicament comprising one or more of these compounds; and a process for preparing such a composition and/or medicament.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows exemplified compounds of the invention.

Figure 2 shows a phylogenetic tree of the SARS-associated coronavirus.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a compound, method and composition for the treatment of a host, and in particular a human or an animal, infected with a (+)-stranded RNA virus that is a coronavirus, such as SARS-CoV, a togavirus, such as a rubivirus (the causative agent for rubella) and an alphavirus (the causative agent for encephalitis), or a picornavirus, such as an enterovirus (particularly Coxsackieviruses, polioviruses, hepatitis A, echoviruses and the four human enterovirus species), a rhinovirus, a cardiovirus and an aphthovirus. This treatment includes administering an effective amount of an anti-coronavirus, anti-togavirus, or anti-picornavirus β-D- or β-L-nucleoside as described herein, or a pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier. The compounds of this invention either possess antiviral activity, or are metabolized to a compound that exhibits such activity.

All coronaviruses, togaviruses and picornaviruses are intended for inclusion within the scope of this invention. In particular, the invention is directed to:

- the SARS-CoV coronavirus;
- human and avian coronaviruses;
- Togaviruses such as, for example, rubiviruses that cause rubella and alphaviruses that cause encephalitis; and
- Picornaviruses, including all four (4) major genera of enteroviruses (particularly Coxsackieviruses, polioviruses, hepatitis A, echoviruses and the four human enterovirus species), rhinoviruses, cardioviruses and aphthoviruses.

The coronaviruses that can be treated according to this invention includes, but are not limited to, human respiratory coronavirus (HCV-229E), porcine transmissible gastroenteritis virus (TGEV), canine coronavirus (CCV), feline enteric coronavirus (FECV), feline infectious peritonitis virus (FIPV), rabbit coronavirus (RbCV), human respiratory coronavirus (HCV-OC43), mouse hepatitis virus (MHV), sialodacryoadnavirus (SDAV), porcine hemagglutinating encephalomyelitis virus (HEV), bovine coronavirus (BCV), rabbit enitis coronavirus (RbEVC), turkey coronavirus (TCV), and avian infectious bronchitis virus (IBV).

Togaviruses that can be treated according to the present invention includes, but are not limited, alphaviruses (such as for example Sindbis virus, Eastern/Western encephalitis viruses, Semliki Forest virus, and Ross River virus) and rubiviruses (such as for example Rubella virus).

Picornaviruses that can be treated according to the present invention includes, but are not limited to, the rhinoviruses (such as for example human rhinoviruses 1A-100, 1B, "Hanks," and bovine rhinoviruses 1, 2, and 3), enteroviruses (such as for example human polioviruses 1, 2, and 3 (A23-echovirus; echo = Enteric Cytopathic Human Orphan viruses) (3 serotypes), human coxsackieviruses A1-22, 24 (23 serotypes), human coxsackieviruses B1-6, human echoviruses 1-7, 9, 11-27, 29, human enteroviruses 68-71 (4 serotypes), vilyuisk virus (1 serotype), simian enteroviruses 1-18 (18 serotypes), bovine enteroviruses 1, 2 (2 serotypes), and porcine enteroviruses 1-8 (8 serotypes)), aphthoviruses (such as for example foot-and-mouth disease virus (FMDV)), cardioviruses(such as for example encephalomyocarditis (EMC) virus, mengovirus, Maus-Elberfield virus, columbia virus, and Theiler's murine encephalocyelitis (TME) virus (TO, GDVII)), hepatoviruses (such as for example human hepatitis virus A), and unassigned (such as for example equine rhinoviruses 1,2, cricket paralysis virus, and the drosophila C virus).

In particular, the present invention provides the following:

a) a pharmaceutical composition comprising a β-D- or β-L-nucleoside compound of the general Formula (AA), (I-XXVIII), a pharmaceutically acceptable salt, ester, salt of

an ester, prodrug, or salt of a prodrug, thereof, optionally with a pharmaceutically acceptable carrier, excipient or diluent;

b) a pharmaceutical composition comprising a β-D- or β-L-nucleoside compound of the general Formula (AA), (I-XXVIII), a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, with one or more other effective antiviral agents (for example other effective anti-coronavirus, such as anti-SARS-CoV, anti-togavirus, such as anti-rubivirus (the causative agent for rubella) and anti-alphavirus (the causative agent for encephalitis), and/or anti-picornavirus, such as anti-enterovirus (particularly Coxsackieviruses, polioviruses, hepatitis A, echoviruses and the four human enterovirus species), anti-rhinovirus, anti-cardiovirus and anti-aphthovirus, or more generally any (+)-RNA active agent), optionally with a pharmaceutically acceptable carrier or diluent;

c) a pharmaceutical composition for the treatment or prophylaxis of a coronavirus, such as SARS-CoV, a togavirus, such as a rubivirus (the causative agent for rubella) and an alphavirus (the causative agent for encephalitis), and/or a picornavirus, such as an enterovirus (particularly Coxsackieviruses, polioviruses, hepatitis A, echoviruses and the four human enterovirus species), a rhinovirus, a cardiovirus and an aphthovirus infection, in a host, such as a mammal, for example a human, especially a host diagnosed as having or being at risk for such infection, comprising a β-D- or β-L-nucleoside compound of the general Formula (AA), (I-XXVIII), a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, optionally with a pharmaceutically acceptable carrier or diluent;

d) a pharmaceutical composition for the treatment or prophylaxis of a coronavirus, such as SARS-CoV, a togavirus, such as a rubivirus (the causative agent for rubella) and an alphavirus (the causative agent for encephalitis), and/or a picornavirus, such as an enterovirus (particularly Coxsackieviruses, polioviruses, hepatitis A, echoviruses and the four human enterovirus species), a rhinovirus, a cardiovirus and an aphthovirus infection, in a host, such as a mammal, for example a human, especially a host diagnosed as having or being at risk for such infection, comprising a β-D- or β-L-nucleoside compound of the general Formula (AA), (I-XXVIII), a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, with one or more other effective antiviral agents (for example other effective anti-coronavirus,

such as anti-SARS-CoV, anti-togavirus, such as anti-rubivirus (the causative agent for rubella) and anti-alphavirus (the causative agent for encephalitis), and/or anti-picornavirus, such as anti-enterovirus (particularly Coxsackieviruses, polioviruses, hepatitis A, echoviruses and the four human enterovirus species), anti-rhinovirus, anti-cardiovirus and anti-aphthovirus, or more generally any (+)-RNA active agent), optionally with a pharmaceutically acceptable carrier or diluent;

e) a pharmaceutical formulation comprising the β-D- or β-L-nucleoside compound of the general Formula (AA), (I-XXVIII), a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, together with a pharmaceutically acceptable carrier, excipient or diluent;

f) a method for the treatment of a coronavirus, such as SARS-CoV, a togavirus, such as a rubivirus (the causative agent for rubella) and an alphavirus (the causative agent for encephalitis), and/or a picornavirus, such as an enterovirus (particularly Coxsackieviruses, polioviruses, hepatitis A, echoviruses and the four human enterovirus species), a rhinovirus, a cardiovirus and an aphthovirus, infection in a host, such as a mammal, for example a human, comprising a β-D- or β-L-nucleoside compound of the general Formula (AA), (I-XXVIII), a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, optionally with a pharmaceutically acceptable carrier, excipient or diluent;

g) a method for the treatment of a coronavirus, such as SARS-CoV, a togavirus, such as a rubivirus (the causative agent for rubella) and an alphavirus (the causative agent for encephalitis), and/or a picornavirus, such as an enterovirus (particularly Coxsackieviruses, polioviruses, hepatitis A, echoviruses and the four human enterovirus species), a rhinovirus, a cardiovirus and an aphthovirus, infection in a host, such as a mammal, for example a human, comprising a β-D- or β-L-nucleoside compound of the general Formula (AA), (I-XXVIII), a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, with one or more other effective antiviral agents, such as one or more other anti-coronavirus, such as anti-SARS-CoV, anti-togavirus, such as anti-rubivirus (the causative agent for rubella) and anti-alphavirus (the causative agent for encephalitis), and/or anti-picornavirus, such as anti-enterovirus (particularly Coxsackieviruses, polioviruses, hepatitis A, echoviruses and the four human enterovirus species), anti-rhinovirus,

anti-cardiovirus and anti-aphthovirus, or more generally any (+)-RNA active agent, optionally with a pharmaceutically acceptable carrier, excipient or diluent;

h) a method for the treatment of a SARS-CoV infection in a host, such as a mammal, for example a human, comprising a β-D- or β-L-nucleoside compound of the general Formula (AA), (I-XXVIII), a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, optionally with a pharmaceutically acceptable carrier, excipient or diluent;

i) a method for the treatment of a SARS-CoV infection in a host, such as a mammal, for example a human, comprising a β-D- or β-L-nucleoside compound of the general Formula (AA), (I-XXVIII), a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, with one or more other effective antiviral agents, such as one or more other anti-coronavirus, such as anti-SARS-CoV, anti-togavirus, such as anti-rubivirus (the causative agent for rubella) and anti-alphavirus (the causative agent for encephalitis), and/or anti-picornavirus, such as anti-enterovirus (particularly Coxsackieviruses, polioviruses, hepatitis A, echoviruses and the four human enterovirus species), anti-rhinovirus, anti-cardiovirus and anti-aphthovirus, or more generally any (+)-RNA active agent, optionally with a pharmaceutically acceptable carrier, excipient or diluent;

j) use of a β-D- or β-L-nucleoside compound of the general Formula (AA), (I-XXVIII), a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, optionally with a pharmaceutically acceptable carrier or diluent, for the treatment of a coronavirus, such as SARS-CoV, a togavirus, such as a rubivirus (the causative agent for rubella) and an alphavirus (the causative agent for encephalitis), and/or a picornavirus, such as an enterovirus (particularly Coxsackieviruses, polioviruses, hepatitis A, echoviruses and the four human enterovirus species), a rhinovirus, a cardiovirus and an aphthovirus infection in a host, such as a mammal, for example a human;

k) use of a β-D- or β-L-nucleoside compound of the general Formula (AA), (I-XXVIII), a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, with one or more other effective antiviral agents, such as an anti-coronavirus, such as anti-SARS-CoV, anti-togavirus, such as anti-rubivirus (the

causative agent for rubella) and anti-alphavirus (the causative agent for encephalitis), and/or anti-picornavirus, such as anti-enterovirus (particularly Coxsackieviruses, polioviruses, hepatitis A, echoviruses and the four human enterovirus species), anti-rhinovirus, anti-cardiovirus and anti-aphthovirus, or more generally any (+)-RNA active agent, optionally with a pharmaceutically acceptable carrier or diluent, for the treatment of a coronavirus, such as SARS-CoV, a togavirus, such as a rubivirus (the causative agent for rubella) and an alphavirus (the causative agent for encephalitis), and/or a picornavirus, such as an enterovirus (particularly Coxsackieviruses, polioviruses, hepatitis A, echoviruses and the four human enterovirus species), a rhinovirus, a cardiovirus and an aphthovirus infection in a host, such as a mammal, for example a human;

l) use of a β-D- or β-L-nucleoside compound of the general Formula (AA), (I-XXVIII), a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, optionally with a pharmaceutically acceptable carrier or diluent, in the manufacture of a medicament for the treatment of a coronavirus, such as SARS-CoV, a togavirus, such as a rubivirus (the causative agent for rubella) and an alphavirus (the causative agent for encephalitis), and/or a picornavirus, such as an enterovirus (particularly Coxsackieviruses, polioviruses, hepatitis A, echoviruses and the four human enterovirus species), a rhinovirus, a cardiovirus and an aphthovirus infection in a host, such as a mammal, for example a human;

m) use of a β-D- or β-L-nucleoside compound of the general Formula (AA), (I-XXVIII), a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, with one or more other effective antiviral agents, such as an anti-coronavirus, such as anti-SARS-CoV, anti-togavirus, such as anti-rubivirus (the causative agent for rubella) and anti-alphavirus (the causative agent for encephalitis), and/or anti-picornavirus, such as anti-enterovirus (particularly Coxsackieviruses, polioviruses, hepatitis A, echoviruses and the four human enterovirus species), anti-rhinovirus, anti-cardiovirus and anti-aphthovirus, or more generally any (+)-RNA active agent, optionally with a pharmaceutically acceptable carrier or diluent, the manufacture of a medicament for the treatment of a coronavirus, such as SARS-CoV, a togavirus, such as a rubivirus (the causative agent for rubella) and an alphavirus (the causative agent for encephalitis), and/or a picornavirus, such as an enterovirus

(particularly Coxsackieviruses, polioviruses, hepatitis A, echoviruses and the four human enterovirus species), a rhinovirus, a cardiovirus and an aphthovirus infection in a host, such as a mammal, for example a human;

n) a β-D- or β-L-nucleoside compound of the general Formula (AA), (I-XXVIII), a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, substantially in the absence of enantiomers of the described nucleoside, or substantially isolated from other chemical entities;

o) a process for the preparation of a β-D- or β-L-nucleoside compound of the general Formula (AA), (I-XXVIII), a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, as provided in more detail below;

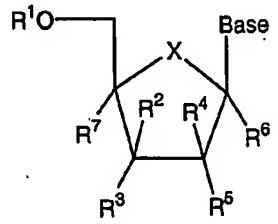
p) a process for the preparation of a β-D- or β-L-nucleoside compound of the general Formula (AA), (I-XXVIII), a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, substantially in the absence of enantiomers of the described nucleoside or substantially isolated from other chemical entities; and

q) a β-D- or β-L-nucleoside compound of the general Formula (AA), (I-XXVIII), or a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof;

I. Active Compounds, Physiologically Acceptable Salts and Prodrugs Thereof

Methods, uses and compositions for the treatment of a coronavirus, such as SARS-CoV, a togavirus, such as a rubivirus (the causative agent for rubella) and an alphavirus (the causative agent for encephalitis), and/or a picornavirus, such as an enterovirus (particularly Coxsackieviruses, polioviruses, hepatitis A, echoviruses and the four human enterovirus species), a rhinovirus, a cardiovirus and an aphthovirus, infection are described that include administering an effective amount of a β-D or β-L-nucleoside of the general formula below, or a pharmaceutically acceptable salt or prodrug thereof.

In a principal embodiment, use of a compound for the treatment of a coronavirus, togavirus or picornavirus is provided wherein the compound is of the formula (AA):



AA

or a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, wherein:

R^1 is H, phosphate or phosphonate (including mono-, di-, or triphosphate or a stabilized phosphate prodrug); optionally substituted acyl (including lower acyl); optionally substituted alkyl (including lower alkyl); optionally substituted sulfonate ester including alkyl or arylalkyl sulfonyl such as methanesulfonyl; optionally substituted aryl; optionally substituted benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of an aryl given herein; optionally substituted arylsulfonyl; a lipid, including a phospholipid; an amino acid derivative; a carbohydrate; a peptide; cholesterol; or other pharmaceutically acceptable leaving group that when administered *in vivo*, provides a compound wherein R^1 is independently H or phosphate;

each R^2 and R^4 independently is H, OH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, halo (F, Cl, Br, or I), NO_2, NH_2, N_3, CH_2N_3, CH_2NH_2, CN, CH_2CN, CH_2N_3, CH_2NHCH_3, $CH_2N(CH_3)_2$, CH_2OH, halogenated alkyl, alkoxy, CF_3, $C(A)_3$, 2-Br-ethyl, CH_2F, CH_2Cl, CH_2CF_3, CF_2CF_3, $CH_2(A)$, $C(A)_2C(A)_3$, SCN, OCN, NCO, haloalkenyl, Br-vinyl, haloalkynyl; $-(CH_2)_mC(O)OR^{13}$, $-(CH_2)_mC(O)SR^{13}$; -O(alkenyl), $-(CH_2)_mNHR^{13}$, $-(CH_2)_mN(R^{13})_2$, $-(CH_2)_mC(O)NHR^{13}$, $-(CH_2)_mC(O)N(R^{13})_2$, $-C(O)OR^{13}$, $-O(R^{13})$, an optionally substituted carbocycle, an optionally substituted heterocycle, an optionally substituted heteroaryl (preferably a heteroaromatic ring having one or more O, S and/or N atoms), or C_{3-7} cycloalkylamino;

each R^3, R^5 and R^6 independently is H, OH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, halo (F, Cl, Br, or I), NO_2, NH_2, N_3, CH_2N_3, CH_2NH_2, CN, CH_2CN, CH_2N_3, CH_2NHCH_3, $CH_2N(CH_3)_2$, CH_2OH, halogenated alkyl, alkoxy, CF_3, $C(A)_3$, 2-Br-ethyl, CH_2F, CH_2Cl, CH_2CF_3, CF_2CF_3, $CH_2(A)$, $C(A)_2C(A)_3$, SCN, OCN, NCO, haloalkenyl, Br-vinyl, haloalkynyl; $-(CH_2)_mC(O)OR^{13}$, $-(CH_2)_mC(O)SR^{13}$; -O(alkenyl), $-(CH_2)_mNHR^{13}$, $-(CH_2)_mN(R^{13})_2$, $-(CH_2)_mC(O)NHR^{13}$, $-(CH_2)_mC(O)N(R^{13})_2$, $-C(O)OR^{13}$, $-O(R^{13})$, an optionally substituted carbocycle (preferably a 3-7 membered carbocyclic ring such as, for example, a C_{3-7} cycloalkylamino), an optionally substituted heterocycle (preferably a 3-7 membered heterocyclic ring having one or more O, S and/or N), an optionally substituted heteroaryl (preferably a heteroaromatic ring having one or more O, S and/or N atoms), a C_{3-7} cycloalkylamino, CF_3, mercapto, optionally substituted C_{1-4} alkyl, C_{1-12} alkoxy, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{2-6} alkenyloxy, C_{1-4} alkylthio, C_{1-8} alkylcarbonyloxy, aryloxycarbonyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, Br-vinyl, -C(O)O(alkyl), O-phosphate or O-phosphonate (including mono-, di-, or triphosphate or a stabilized phosphate prodrug); O-acyl (including lower acyl); O-alkyl (including lower alkyl); O-sulfonate ester including O-alkyl or O-arylalkyl sulfonyl including O-methanesulfonyl; O-aryl; O-benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of an aryl given herein; -OC(O)O-aryl; -OC(O)O-aralkyl; -S(acyl); -S(alkyl); -S(alkenyl); optionally substituted O-arylsulfonyl; an O-linked lipid, including an O-phospholipid; an O-linked amino acid; an O-linked carbohydrate; an O-linked peptide; O-linked cholesterol; or other O-linked pharmaceutically acceptable leaving group that when administered *in vivo*, provides independently OH or O-phosphate;

each R^7 is independently H, $-OR^1$, -OH, $-NO_2$, $-CF_3$, $-NH_2$, Cl, F, Br, I, N_3, CN, optionally substituted alkyl, optionally substituted alkenyl or alkynyl, Br-vinyl, $-CH_2OH$, -O(R), alkoxy, $-(CH_2)_mC(O)O(R)$, -OC(O)O-aryl, -OC(O)O-aralkyl, -SR, $-(CH_2)_mNHR$, $-(CH_2)_mN(R)_2$, or C_{3-7} cycloalkylamino;

each R is H, alkyl, alkenyl, alkynyl, acyl, aryl or aralkyl;

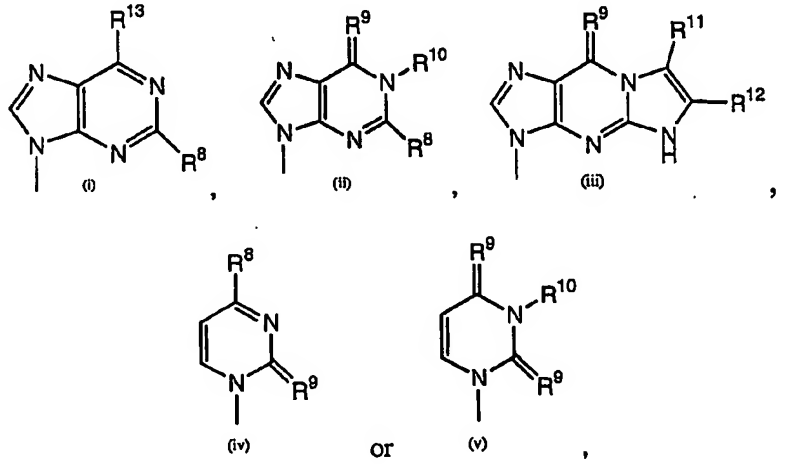
X is O, S, SO_2, CH_2, or CHOH;

m is 0, 1 or 2;

R^{13} is H, alkyl, alkenyl, alkynyl, acyl, aryl or aralkyl;

A is H, OH, C_{1-4} alkyl, halo (F, Cl, Br, or I), azido, cyano, C_{2-6} alkenyl, C_{2-6} alkynyl, Br-vinyl, 2-Br-ethyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), CF_3, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, or -N(acyl)$_2$; and

Base is as defined in the specification, including a purine or pyurimidine base or a compound including but not limited to:



wherein:

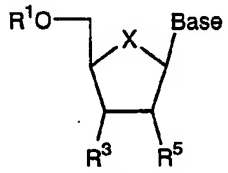
each R^8, R^{10}, R^{11}, R^{12} and R^{13} independently is H, NH_2, SH, CF_3, halo, NO_2, N_3, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl (preferably optionally substituted phenyl), -NH-cycloalkyl, -NH-cycloalkenyl, -NH-heterocycle, -NH-heteroaryl, -O-cycloalkyl, -O-cycloalkenyl, -O-heterocycle, -O-heteroaryl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{3-6} cycloalkylamino, C_{1-4} alkyl-C(=O)OH, C_{1-4} alkyl-C(=O)O-aryl (preferably C_{1-4} alkyl-C(=O)O-phenyl), C_{1-4} alkyl-C(=O)O-heterocycle, C_{1-4} alkyl-C(=O)O-heteroaryl, or C_{1-4} alkoxy; and

R^9 is O or S;

and all tautomeric, enantiomeric and stereoisomeric forms thereof.

In another embodiment, methods and compositions for the treatment of SARS-CoV, coronavirus, togaviruses, and/or picornaviruses infection, or more generally any (+)-RNA viral infection, are described that include administering an effective amount of a β-D or β-L-nucleoside of the Formulae (I) – (XXVIII), or a pharmaceutically acceptable salt or prodrug thereof.

In a yet another embodiment, use of a compound for the treatment of a coronavirus, togavirus or picornavirus is provided wherein the compound is of the formula (I):



(I)

or a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, wherein:

R^1 is H, phosphate or phosphonate (including mono-, di-, or triphosphate or a stabilized phosphate prodrug); optionally substituted acyl (including lower acyl); optionally substituted alkyl (including lower alkyl); optionally substituted sulfonate ester including alkyl or arylalkyl sulfonyl such as methanesulfonyl; optionally substituted aryl; optionally substituted benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of an aryl given herein; optionally substituted arylsulfonyl; a lipid, including a phospholipid; an amino acid derivative; a carbohydrate; a peptide; cholesterol; or other pharmaceutically acceptable leaving group that when administered *in vivo*, provides a compound wherein R^1 is independently H or phosphate;

each R^3 and R^5 independently is H, OH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, halo (F, Cl, Br, or I), NO_2, NH_2, N_3, CH_2N_3, CH_2NH_2, CN, CH_2CN, CH_2N_3, CH_2NHCH_3, $CH_2N(CH_3)_2$, CH_2OH, halogenated alkyl, alkoxy, CF_3, $C(A)_3$, 2-Br-ethyl, CH_2F, CH_2Cl,

CH_2CF_3, CF_2CF_3, $CH_2(A)$, $C(A)_2C(A)_3$, SCN, OCN, NCO, haloalkenyl, Br-vinyl, haloalkynyl; $-(CH_2)_mC(O)OR^{13}$, $-(CH_2)_mC(O)SR^{13}$; -O(alkenyl), $-(CH_2)_mNHR^{13}$, $-(CH_2)_mN(R^{13})_2$, $-(CH_2)_mC(O)NHR^{13}$, $-(CH_2)_mC(O)N(R^{13})_2$, $-C(O)OR^{13}$, $-O(R^{13})$, an optionally substituted carbocycle (preferably a 3-7 membered carbocyclic ring such as, for example, a C_{3-7} cycloalkylamino), an optionally substituted heterocycle (preferably a 3-7 membered heterocyclic ring having one or more O, S and/or N), an optionally substituted heteroaryl (preferably a heteroaromatic ring having one or more O, S and/or N atoms), a C_{3-7} cycloalkylamino, CF_3, mercapto, optionally substituted C_{1-4} alkyl, C_{1-12} alkoxy, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{2-6} alkenyloxy, C_{1-4} alkylthio, C_{1-8} alkylcarbonyloxy, aryloxycarbonyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, Br-vinyl, -C(O)O(alkyl), O-phosphate or O-phosphonate (including mono-, di-, or triphosphate or a stabilized phosphate prodrug); O-acyl (including lower acyl); O-alkyl (including lower alkyl); O-sulfonate ester including O-alkyl or O-arylalkyl sulfonyl including O-methanesulfonyl; O-aryl; O-benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of an aryl given herein; -OC(O)O-aryl; -OC(O)O-aralkyl; -S(acyl); -S(alkyl); -S(alkenyl); optionally substituted O-arylsulfonyl; an O-linked lipid, including an O-phospholipid; an O-linked amino acid; an O-linked carbohydrate; an O-linked peptide; O-linked cholesterol; or other O-linked pharmaceutically acceptable leaving group that when administered *in vivo*, provides independently OH or O-phosphate;

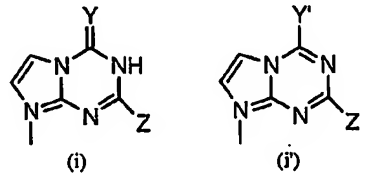
X is O, S, SO_2, CH_2, CHOH, CH-halogen, C-(halogen)$_2$;

m is 0, 1 or 2;

R^4 is H, alkyl, alkenyl, alkynyl, acyl, aryl or aralkyl;

A is H, OH, C_{1-4} alkyl, halo, azido, cyano, C_{2-6} alkenyl, C_{2-6} alkynyl, Br-vinyl, 2-Br-ethyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), CF_3, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, or –N(acyl)$_2$; and

Base is defined in the specification, including but not limited to:



(i) (i')

wherein:

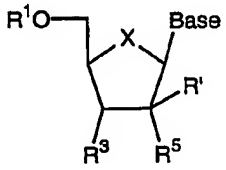
Y is O or S;

Y' is H, OH, SH, NH_2, halo, CF_3, C_{1-4} alkyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{3-6} cycloalkylamino, or C_{1-4} alkoxy;

Z is H, NH_2, CF_3, C_{1-4} alkyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, or C_{3-6} cycloalkylamino, and

all tautomeric, enantiomeric and stereoisomeric forms thereof.

In another embodiment, use of a compound for the treatment of a coronavirus, togavirus or picornavirus is provided wherein the compound is of the formula (II):



(II)

or a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, wherein:

R^1, R^3, and R^5 are defined as above;

R' is H, OH, SH, halo (F, Cl, Br, or I), optionally substituted C_{1-4} alkyl, optionally substituted C_{2-4} alkenyl or C_{2-4} alkynyl, N_3, CN, CH_2CN, CH_2N_3, CH_2NH_2, CH_2NHCH_3, $CH_2N(CH_3)_2$, CH_2OH, halogenated alkyl, alkoxy, CF_3, $C(A)_3$, 2-Br-ethyl, CH_2F, CH_2Cl, CH_2CF_3, CF_2CF_3, $CH_2(A)$, $C(A)_2(A)_3$, haloalkenyl, Br-vinyl, haloalkynyl; $-(CH_2)_mC(O)OR^4$, -O(acyl), -O(lower acyl), -O(alkyl),

-O(lower alkyl), -O(alkenyl), $-NO_2$, $-NH_2$, $-(CH_2)_mNHR^4$, $-(CH_2)_mN(R^4)_2$, $-(CH_2)_mC(O)NHR^4$, $-(CH_2)_mC(O)N(R^4)_2$, or C_{3-7} cycloalkylamino, and where the optional substitutions on alkyl, alkenyl and/or alkynyl may be one or more halogen, hydroxy, amino, alkoxy, or alkylthio groups or atoms taken in any combination; or alternatively

R' and R^5, together with the carbon atom to which they are attached, form an optionally substituted 3- to 6-membered saturated or unsaturated ring that optionally may have one or more heteroatoms selected from the group consisting of O, S, N, or P;

A is H, OH, C_{1-4} alkyl, halo (F, Cl, Br, or I), azido, cyano, C_{2-6} alkenyl, C_{2-6} alkynyl, Br-vinyl, 2-Br-ethyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), CF_3, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, or $-N(acyl)_2$;

m is 0, 1 or 2;

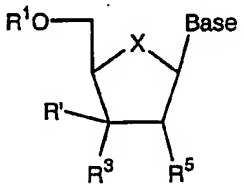
R^4 is H, alkyl, alkenyl, alkynyl, or acyl;

X is defined as above; and

Base is as in the specification; and

all tautomeric, enantiomeric and stereoisomeric forms thereof.

In another embodiment, the use of a compound for the treatment of a coronavirus, togavirus or picornavirus is provided wherein the compound is of the formula (III):



(III)

or a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, wherein:

R^1, R^3, R^5, R' and A are all as defined above; or

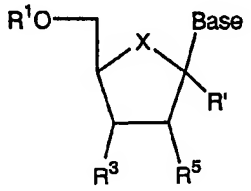
R' and R^3, together with the carbon atom to which they are attached, form an optionally substituted 3- to 6-membered saturated or unsaturated ring that optionally may have one or more heteroatoms selected from the group consisting of O, S, N, or P;

X is defined as above; and

Base is as defined in the specification; and

all tautomeric, enantiomeric and stereoisomeric forms thereof.

In another embodiment, the use of a compound for the treatment of a coronavirus, togavirus or picornavirus is provided wherein the compound is of the formula (IV):



(IV)

or a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, wherein:

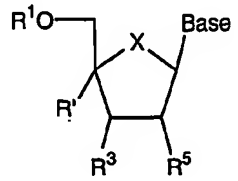
R^1, R^3, R^5, and R' are all as defined above, except that R' is –OH, -SH or $–NH_2$ only when X is C;

X is as defined above; and

Base is as defined in the specification; and

all tautomeric, enantiomeric and stereoisomeric forms thereof.

In another embodiment, the use of a compound for the treatment of a coronavirus, togavirus or picornavirus is provided wherein the compound is of the formula (V):



(V)

or a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, wherein:

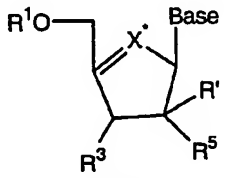
R^1, R^3, R^5, and R' are all as defined above;

X is as defined above; and

Base is as defined in the specification; and

all tautomeric, enantiomeric and stereoisomeric forms thereof.

In another embodiment, the use of a compound for the treatment of a coronavirus, togavirus or picornavirus is provided wherein the compound is of the formula (VI):



(VI)

or a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, wherein:

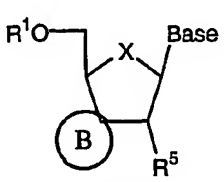
R^1, R^3, R^5 and R' are all as defined above;

X^* is CH, C-OH, or C-halogen (wherein halogen includes F, Cl, Br, and I); and

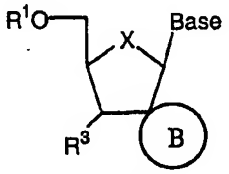
Base is as defined in the specification; and

all tautomeric, enantiomeric and stereoisomeric forms thereof.

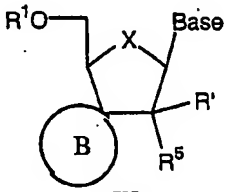
In another embodiment, the use of a compound for the treatment of a coronavirus, togavirus or picornavirus is provided wherein the compound is of the formulas (VII), (VIII), (IX), or (X):



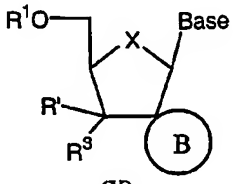
(VII),



(VIII),



(IX)



or (X),

or a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, wherein:

R^1, R^3, R^5, R' are all as defined above;

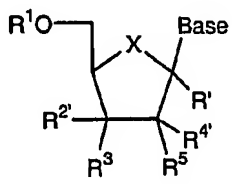
X is defined as above;

(B) is an optionally substituted carbocycle (preferably a 3-7 membered carbocyclic ring) or an optionally substituted heterocycle (preferably a 3-7 membered heterocyclic ring having one or more O, S, and/or N); and

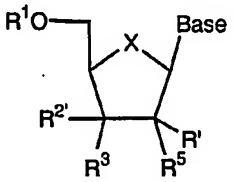
Base is as defined in the specification; and

all tautomeric, enantiomeric and stereoisomeric forms thereof.

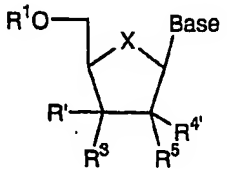
In another embodiment, the use of a compound for the treatment of a coronavirus, togavirus or picornavirus is provided wherein the compound is of the formulae (XI), (XII), (XIII), or (XIV):



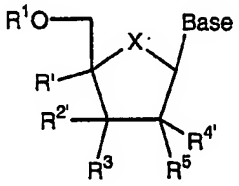
(XI)



(XII)



(XIII)



or (XIV)

or a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, wherein:

R^1, R^3, R^5, and R' are all as defined above, except that R' in Formula (XI) is -OH, $-NH_2$ or -SH only when X is C;

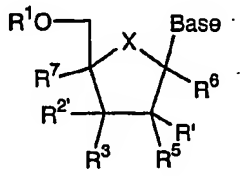
X is as defined above;

Each $R^{2'}$ and $R^{4'}$, independently, is H, -OH, -SH, $-NH_2$, $-CF_3$, Cl, F, Br, I, optionally substituted alkyl, optionally substituted alkenyl or alkynyl, $-CH_2OH$, alkoxy, CH_2F, CH_2N_3, CH_2CN, $-(CH_2)_mC(O)OR^4$, $-(CH_2)_mC(O)NHR^4$, $-(CH_2)_mC(O)N(R^4)_2$, -NH(alkyl), $-N(alkyl)_2$, -NH(acyl), $-N(acyl)_2$, or C_{3-7} cycloalkylamino; and

Base is as defined in the specification; and

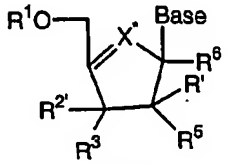
all tautomeric, enantiomeric and stereoisomeric forms thereof.

In another embodiment, the use of a compound for the treatment of a coronavirus, togavirus or picornavirus is provided wherein the compound is of the formulae (XV) or (XVI):



(XV)

or



(XVI)

or a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, wherein:

R^1, $R^{2'}$, R^3, R^5, R^6, and R' are all as defined above, except that R^6 is -OH, $-NH_2$ or -SH only when X is C;

X and X* are as defined above;

each R^7 is independently H, $-OR^1$, -OH, $-NO_2$, $-CF_3$, $-NH_2$, Cl, F, Br, I, N_3, CN, optionally substituted alkyl, optionally substituted alkenyl or alkynyl, Br-vinyl, $-CH_2OH$, -O(R), alkoxy, $-(CH_2)_mC(O)O(R)$, -OC(O)O-aryl, -OC(O)O-aralkyl, -SR, $-(CH_2)_mNHR$, $-(CH_2)_mN(R)_2$, or C_{3-7} cycloalkylamino;

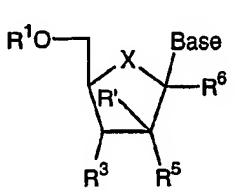
each R is H, alkyl, alkenyl, alkynyl, acyl, aryl or aralkyl;

m is 0, 1 or 2; and

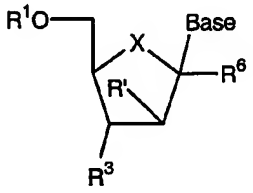
Base is as defined in the specification; and

all tautomeric, enantiomeric and stereoisomeric forms thereof.

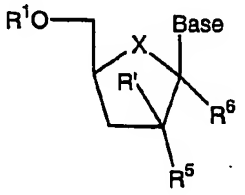
In another embodiment, the use of a compound for the treatment of a coronavirus, togavirus or picornavirus is provided wherein the compound is of the formula (XVII), (XVIII), (XIX), (XX), (XXI), (XXII), (XXIII), (XXIV), (XXV), (XXVI), (XXVII), or (XXVIII):



(XVII) ,



(XVIII) ,



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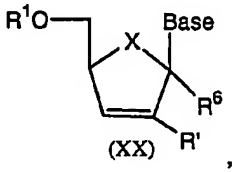
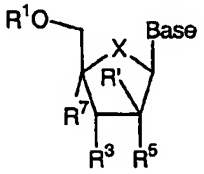
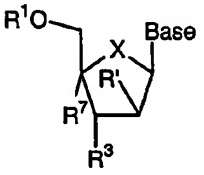


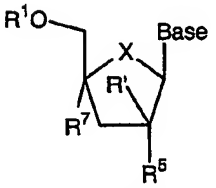
(XX) ,



(XXI) ,



(XXII) ,



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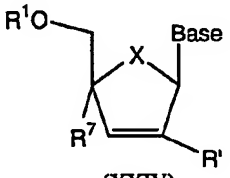

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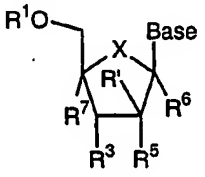

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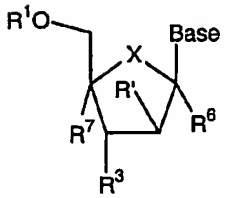
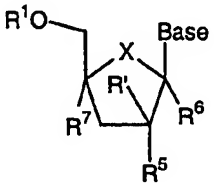
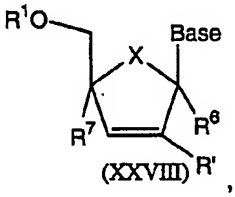


(XXVI) ,



(XXVII) , or



(XXVIII) ,

or a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, wherein:

R^1, R^3, R^5, R^6, R^7, and R' are all as defined above, except that R^6 is -OH, $-NH_2$ or -SH only when X is C;

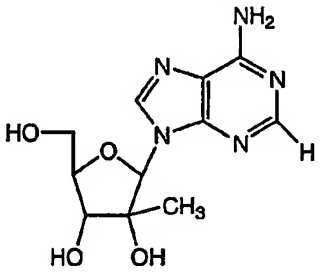
X is defined as above;

m is 0, 1 or 2; and

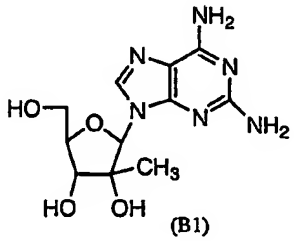
Base is as defined in the specification; and

all tautomeric, enantiomeric and stereoisomeric forms thereof.

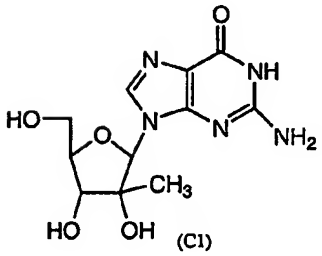
In another particular embodiment of the present invention, the use of a compound for the treatment of a coronavirus, togavirus or picornavirus is provided wherein the compound is of the formulas A1-N1:



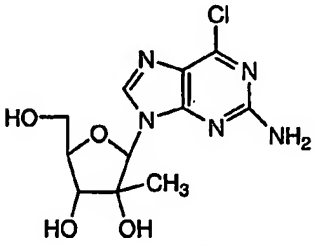
(A1)



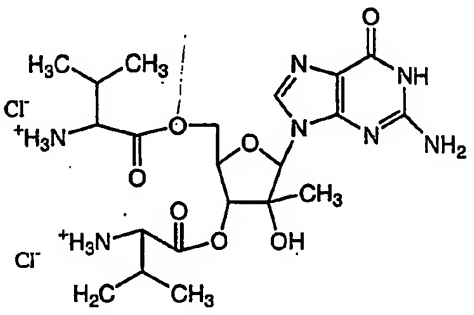
(B1)



(C1)



(D1)



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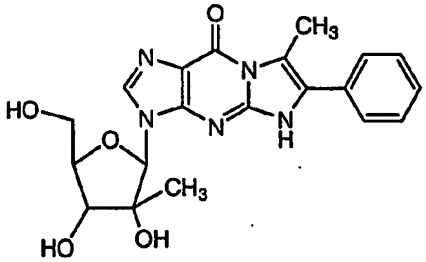
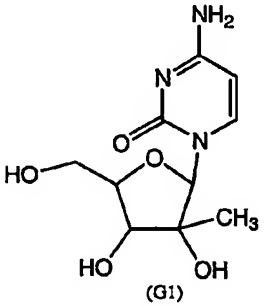
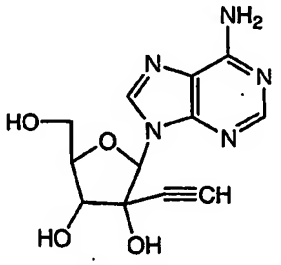


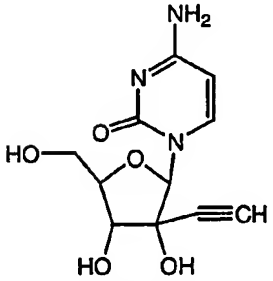
(F1)



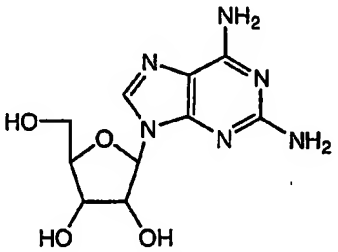
(G1)



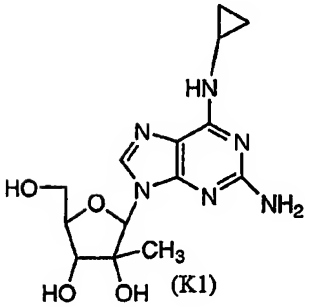
(H1)



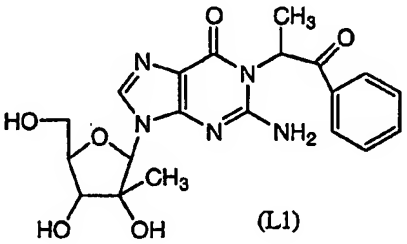
(I1)



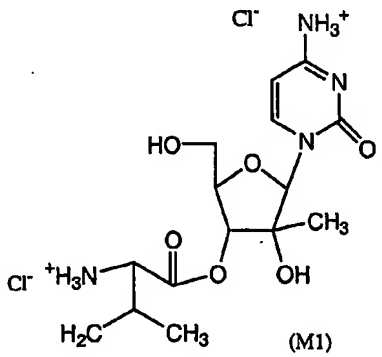
(J1)



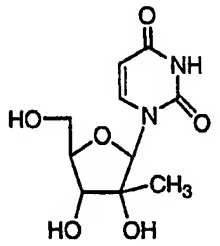
(K1)



(L1)



(M1)



(N1)

In a particular embodiment of the invention, the compound of the present invention is in the form of its 2', 3', and/or 5'-prodrug. In one embodiment, the compound is a prodrug that includes biologically cleavable moieties at the 2', 3' and/or 5' positions. In one embodiment, the compound is an acyl prodrug with biologically cleavable acyl moieties at the 2', 3' and/or 5' positions. In a particular embodiment, the compound is an amino acid ester prodrug with biologically cleavable amino acid moieties at the 2', 3' and/or 5' positions. Preferred moieties are amino acid esters including valyl, and alkyl esters including acetyl. Therefore, this invention specifically includes the 2'-L-amino acid ester, 3'-L-amino acid ester, 2',5'-L-diamino acid ester, and 3',5'-L-diamino acid ester of the nucleosides of the present invention; and the 2'-ester, 3'-ester, 2',5'-diester and 3',5'-diester of the nucleosides wherein (i) the 2' and/or 3' ester is an amino acid ester and the 5'-ester is an alkyl or aryl ester; (ii) both esters are amino acid esters; (iii) both esters are independently alkyl or aryl esters; and (iv) the 2' and/or 3' ester is independently an alkyl or aryl ester and the 5'-ester is an amino acid ester.

The active compounds of the present invention can be administered alone or in combination, alternation or sequential steps with another anti-coronavirus, such as anti-SARS-CoV, anti-togavirus, such as anti-rubivirus (the causative agent for rubella) and anti-alphavirus (the causative agent for encephalitis), and/or anti-picornavirus, such as anti-enterovirus (particularly Coxsackieviruses, polioviruses, hepatitis A, echoviruses and the four human enterovirus species), anti-rhinovirus, anti-cardiovirus and anti-aphthovirus, or more generally any (+)-RNA active agent. In combination therapy, effective dosages of two or more agents are administered together, whereas in alternation

or sequential-step therapy, an effective dosage of each agent is administered serially or sequentially. The dosages given will depend on absorption, inactivation and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions. In preferred embodiments, an anti-SARS-CoV, anti-coronavirus, anti-togavirus, and/or anti-picornavirus compound that exhibits an EC_{50} of 10-15 μM or less, or preferably less than 1-5 μM, is desirable.

The active compound can be administered as any salt or prodrug that upon administration to the recipient is capable of providing directly or indirectly the parent compound, or that exhibits activity itself. Nonlimiting examples are the pharmaceutically acceptable salts, which are alternatively referred to as "physiologically acceptable salts", and a compound that has been alkylated or acylated at the 3'- or 5'-position or on the purine or pyrimidine base, thereby forming a type of "pharmaceutically acceptable prodrug". Further, the modifications can affect the biological activity of the compound, in some cases increasing the activity over the parent compound. This can easily be assessed by preparing the salt or prodrug and testing its antiviral activity according to the methods described herein, or other methods known to those skilled in the art.

II. Definitions

The term "alkyl" as used herein, unless otherwise specified, includes a saturated straight, branched, or cyclic, primary, secondary, or tertiary hydrocarbon of typically C_1 to C_{10}, and specifically includes methyl, trifluoromethyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, *t*-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, cyclohexylmethyl, 3-methylpentyl, 2,2-dimethybutyl, and 2,3-dimethylbutyl. The term includes both substituted and unsubstituted alkyl groups. Moieties with which the alkyl group can be substituted with one or more substituents include but are not limited to halo, including Cl, F, Br and I so as to form, for eg., CF_3, 2-

Br-ethyl, CH_2F, CH_2Cl, CH_2CF_3, or CF_2CF_3; hydroxyl, for eg. CH_2OH; amino, for eg., CH_2NH_2, CH_2NHCH_3, or $CH_2N(CH_3)_2$; carboxylate; carboxamido; alkylamino; arylamino; alkoxy; aryloxy; nitro; azido, for eg., CH_2N_3; cyano, for eg., CH_2CN; thio; sulfonic acid; sulfate; phosphonic acid; phosphate; and phosphonate, either unprotected or protected as necessary, known to those skilled in the art, for eg., as taught in Greene et al., *Protective Groups in Organic Synthesis*, John Wiley and Sons, Second Edition (1991), incorporated herein by reference.

The term "lower alkyl" as used herein, and unless otherwise specified, includes a C_1 to C_6 saturated straight, branched, or if appropriate, cyclic as in cyclopropyl, for eg., alkyl group, including both substituted and unsubstituted forms. Unless otherwise specifically stated in this application, when alkyl is a suitable moiety, lower alkyl is preferred. Similarly, when alkyl or lower alkyl is a suitable moiety, unsubstituted alkyl or lower alkyl is preferred.

The terms "alkylamino" and "arylamino" refer to an amino group that has one or two alkyl or aryl substituents, respectively.

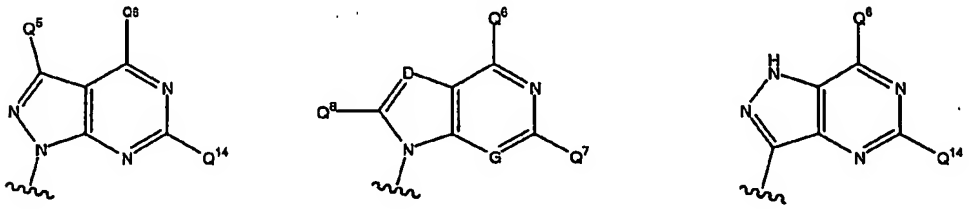
The term "protected" as used herein and, unless otherwise defined, includes a group that is added to an oxygen, nitrogen or phosphorus atom to prevent its further reaction or for other purposes. Numerous oxygen and nitrogen protecting groups are known to those skilled in the art of organic synthesis.

The term "aryl" as used herein and, unless otherwise specified, includes phenyl, biphenyl or naphthyl, and preferably phenyl. The term includes both substituted and unsubstituted moieties. The aryl group can be substituted with one or more moieties including but not limited to alkyl, hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, thio, alkylthio, carboxamido, carboxylate, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected or protected as necessary, as known to those skilled in the art, for eg., as taught in Greene et al., *Protective Groups in Organic Synthesis*, John Wiley and Sons, Second Edition (1991), incorporated herein by reference.

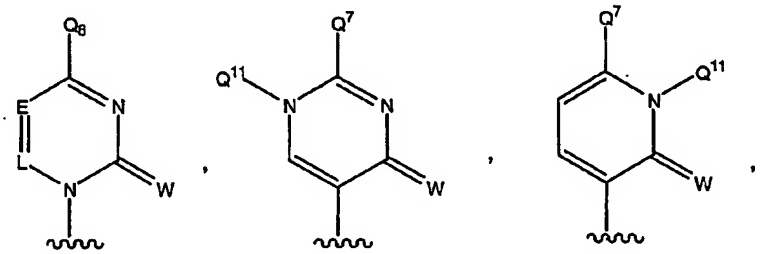
The terms "alkaryl" and "akylaryl" refer to an alkyl group with an aryl sustituent. The terms "aralkyl" and "arylalkyl" refer to an aryl group with an alkyl substituent.

The term "halo" as used herein includes bromo, chloro, iodo and fluoro.

The term base refers to any purine or pyrimidine base including, but not limited to, adenine, N^6-alkylpurines, N^6-acylpurines (wherein acyl is C(O)(alkyl, aryl, alkylaryl, or arylalkyl), N^6-benzylpurine, N^6-halopurine, N^6-vinylpurine, N^6-acetylenic purine, N^6-acyl purine, N^6-hydroxyalkyl purine, N^6-thioalkyl purine, N^2-alkylpurines, N^2-alkyl-6-thiopurines, thymine, cytosine, 5-fluorocytosine, 5-methylcytosine, 6-azapyrimidine, including 6-azacytosine, 2- and/or 4-mercaptopyrmidine, uracil, 5-halouracil, including 5-fluorouracil, C^5-alkylpyrimidines, C^5-benzylpyrimidines, C^5-halopyrimidines, C^5-vinylpyrimidine, C^5-acetylenic pyrimidine, C^5-acyl pyrimidine, C^5-hydroxyalkyl purine, C^5-amidopyrimidine, C^5-cyanopyrimidine, C^5-nitropyrimidine, C^5-amino-pyrimidine, N^2-alkylpurines, N^2-alkyl-6-thiopurines, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl,



(i) (ii) (iii)



(iv) (v) (vi)

wherein:

each G and L is independently CH or N;

each D is independently N, CH, C-CN, C-NO_2, C-C_{1-3} alkyl, C-$NHCONH_2$, C-$CONQ^{11}Q^{11}$, C-$CSNQ^{II}Q^{II}$, $CCOOQ^{11}$, C-$C(=NH)NH_2$, C-hydroxy, C-C_{1-3}alkoxy,C-amino, C-C_{1-4} alkylamino, C-di(C_{1-4} alkyl)amino, C-halogen, C-(1,3-oxazol-2-yl), C-(1,3-thiazol-2-yl), or C-(imidazol-2-yl); wherein alkyl is

unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and C_{1-3} alkoxy;

each E is independently N or CQ^5;

each W is independently O, S, or NR;

each R is independently H, OH, alkyl;

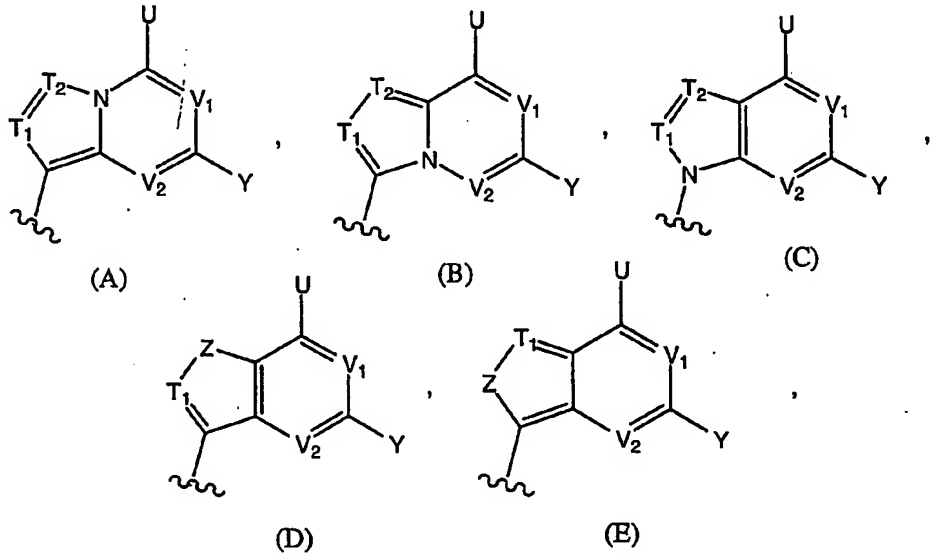
each Q^6 is independently H, OH, SH, NH_2, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{3-6} cycloalkylamino, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, or CF_3;

each Q^5 is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} alkylamino, CF_3, halogen, N, CN, NO_2, $NHCONH_2$, $CONQ^{11}Q^{11}$, $CSNQ^{11}Q^{11}$, $COOQ^{11}$, $C(=NH)NH_2$, hydroxy, C_{1-3}alkoxy,amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, halogen, 1,3-oxazol-2-yl, 1,3-thiazol-2-yl, or imidazol-2-yl; wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and C_{1-3} alkoxy;

each Q^7 and Q^{14} is independently selected from the group consisting of H, CF_3, OH, SH, OR, SR C_{1-4} alkyl, amino, C_{1-4} alkylamino, C_{3-6} cycloalkylamino, and di(C_{1-4} alkyl)amino;

each Q^{11} is independently H or C_{1-6} alkyl;

each Q^8 is independently H, halogen, CN, carboxy, C_{1-4} alkyloxycarbonyl, N_3, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, (C_{1-4} alkyl)0-2 aminomethyl, N, CN, NO_2, C_{1-3} alkyl, $NHCONH_2$, $CONQ^{11}Q^{11}$, $CSNQ^{11}Q^{11}$, $COOQ^{11}$, $C(=NH)NH_2$, 1,3-oxazol-2-yl, 1,3-thiazol-2-yl, or imidazol-2-yl, wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and C_{1-3} alkoxy;



(A) (B) (C) (D) (E)

wherein:

each T_1 and T_2 is independently selected from N, CH, or C-Q^{16};

each Q^{16}, U, and Y is independently selected from is H, OH, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, cycloalkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, OR^4, NR^4R^5 or SR^5, Br-vinyl, -O-alkyl, -O-alkenyl, -O-alkynyl, -O-aryl, -O-aralkyl, -O-acyl, -O-cycloalkyl, NH_2, NH-alkyl, N-dialkyl, NH-acyl, N-aryl, N-aralkyl, NH-cycloalkyl, SH, S-alkyl, S-acyl, S-aryl, S-cycloalkyl, S-aralkyl, CN, N_3, COOH, $CONH_2$, CO_2-alkyl, CONH-alkyl, CON-dialkyl, OH, CF_3, CH_2OH, $(CH_2)_mOH$, $(CH_2)_mNH_2$, $(CH_2)_mCOOH$, $(CH_2)_mCN$, $(CH_2)_mNO_2$, $(CH_2)_mCONH_2$, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{3-6} cycloalkylamino, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, (C_{1-4} alkyl)$_{0-2}$ aminomethyl, or-$NHC(=NH)NH_2$;

each R^4 and R^5 is independently selected from hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl);

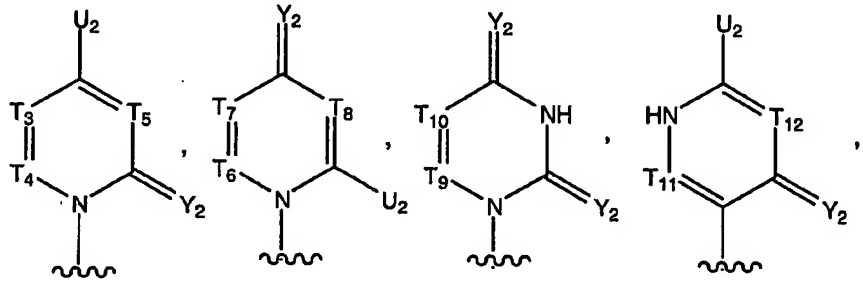
each m is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

each Z is independently S, SO, SO_2, C=O, or NQ^{20};

each Q^{20} is independently H or alkyl; and

each V_1 and V_2 is independently selected from CH or N;

or



(F) (G) (H) (I)

wherein:

each T_3 and T_4 is independently selected from N or CQ^{22};

each Q^{22} is independently selected from H, OH, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, cycloalkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, OR^4, NR^4R^5 or SR^5, Br-vinyl, -O-alkyl, -O-alkenyl, -O-alkynyl, -O-aryl, -O-aralkyl, -O-acyl, -O-cycloalkyl, NH_2, NH-alkyl, N-dialkyl, NH-acyl, N-aryl, N-aralkyl, NH-cycloalkyl, SH, S-alkyl, S-acyl, S-aryl, S-cycloalkyl, S-aralkyl, CN, N_3, COOH, $CONH_2$, CO_2-alkyl, CONH-alkyl, CON-dialkyl, OH, CF_3, CH_2OH, $(CH_2)_mOH$, $(CH_2)_mNH_2$, $(CH_2)_mCOOH$, $(CH_2)_mCN$, $(CH_2)_mNO_2$, $(CH_2)_mCONH_2$, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{3-6} cycloalkylamino, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, (C_{1-4} alkyl)$_{0-2}$ aminomethyl, or -NHC(=NH)NH_2;

T_5 is NH;

each R^4 and R^5 is independently selected from hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl);

each m is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

each T_6, T_7, T_8, T_9, T_{10}, T_{11}, and T_{12} is independently selected from N or CH;

each U_2 is independently H, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, OR^4, NR^4R^5 or SR^5;

each Y_2 is independently O, S, NH, NR or $CQ^{24}Q^{26}$ where R is H, OH, or alkyl;

each Q^{24} and Q^{26} is independently selected from H, alkyl, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, OR^4, NR^4R^5 or SR^5.

Further examples of purine bases include, but are not limited to, guanine, adenine, hypoxanthine, 2,6-diaminopurine, and 6-chloropurine. Functional oxygen and nitrogen groups on the base can be protected as necessary or desired. Suitable protecting groups are well known to those skilled in the art, and include trimethylsilyl, dimethylhexylsilyl, *t*-butyldimethylsilyl, and *t*-butyldiphenylsilyl, trityl, alkyl groups, and acyl groups such as acetyl and propionyl, methanesulfonyl, and p-toluenesulfonyl.

The term "acyl" includes a carboxylic acid ester in which the non-carbonyl moiety of the ester group is selected from straight, branched, or cyclic alkyl or lower alkyl; alkoxyalkyl including methoxymethyl; aralkyl including benzyl; aryloxyalkyl such as phenoxymethyl; aryl including phenyl optionally substituted with halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy; sulfonate esters such as alkyl or aralkyl sulphonyl including methanesulfonyl; the mono-, di- or triphosphate ester; trityl or monomethoxytrityl; substituted benzyl; trialkylsilyl as, for eg., dimethyl-*t*-butylsilyl or diphenylmethylsilyl. Aryl groups in the esters optimally comprise a phenyl group.

The term "acyl" or O-linked ester refers to a group of the formula C(O)R', wherein R' is an straight, branched, or cyclic alkyl (including lower alkyl), carboxylate residue of an amino acid, aryl including phenyl, heteroaryl, alkaryl, aralkyl including

benzy l, alkoxyalkyl including methoxymethyl, aryloxyalkyl such as phenoxymethyl; or substituted alkyl (including lower alkyl), aryl including phenyl optionally substituted with chloro, bromo, fluoro, iodo, C_1 to C_4 alkyl or C_1 to C_4 alkoxy, sulfonate esters such as alkyl or aralkyl sulphonyl including methanesulfonyl, the mono, di or triphosphate ester, trityl or monomethoxy-trityl, substituted benzyl, alkaryl, aralkyl including benzyl, alkoxyalkyl including methoxymethyl, aryloxyalkyl such as phenoxymethyl. Aryl groups in the esters optimally comprise a phenyl group. In nonlimiting embodiments, acyl groups include acetyl, trifluoroacetyl, methylacetyl, cyclopropylacetyl, cyclopropyl-carboxy, propionyl, butyryl, isobutyryl, hexanoyl, heptanoyloctanoyl, neo-heptanoyl, phenylacetyl, 2-acetoxy-2-phenylacetyl, diphenylacetyl, α-methoxy-α-trifluoromethyl-phenylacetyl, bromoacetyl, 2-nitro-benzeneacetyl, 4-chloro-benzeneacetyl, 2-chloro-2,2-diphenylacetyl, 2-chloro-2-phenylacetyl, trimethylacetyl, chlorodifluoroacetyl, perfluoroacetyl, fluoroacetyl, bromodifluoroacetyl, methoxyacetyl, 2-thiopheneacetyl, chlorosulfonylacetyl, 3-methoxyphenylacetyl, phenoxyacetyl, tert-butylacetyl, trichloroacetyl, monochloro-acetyl, dichloroacetyl, 7H-dodecafluoro-heptanoyl, perfluoro-heptanoyl, 7H-dodeca-fluoroheptanoyl, 7-chlorododecafluoro-heptanoyl, 7-chloro-dodecafluoro-heptanoyl, 7H-dodecafluoroheptanoyl, 7H-dodeca-fluoroheptanoyl, nona-fluoro-3,6-dioxa-heptanoyl, nonafluoro-3,6-dioxaheptanoyl, perfluoroheptanoyl, methoxybenzoyl, methyl 3-amino-5-phenylthiophene-2-carboxyl, 3,6-dichloro-2-methoxy-benzoyl, 4-(1,1,2,2-tetrafluoro-ethoxy)-benzoyl, 2-bromo-propionyl, omega-aminocapryl, decanoyl, n-pentadecanoyl, stearyl, 3-cyclopentyl-propionyl, 1-benzene-carboxyl, O-acetylmandelyl, pivaloyl acetyl, 1-adamantane-carboxyl, cyclohexane-carboxyl, 2,6-pyridinedicarboxyl, cyclopropane-carboxyl, cyclobutane-carboxyl, perfluorocyclohexyl carboxyl, 4-methylbenzoyl, chloromethyl isoxazolyl carbonyl, perfluorocyclohexyl carboxyl, crotonyl, 1-methyl-1H-indazole-3-carbonyl, 2-propenyl, isovaleryl, 1-pyrrolidinecarbonyl, 4-phenylbenzoyl.

The term "lower acyl" includes an acyl group in which the non-carbonyl moiety is lower alkyl.

The term amino acid includes naturally occurring and synthetic α, β, γ, or δ amino acids, and includes but is not limited to, amino acids found in proteins, *i.e.* glycine, alanine, valine, leucine, isoleucine, methionine, phenylalanine, tryptophan, proline, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartate, glutamate,

lysine, arginine and histidine. In a preferred embodiment, the amino acid is in the L-configuration, but can also be used in the D-configuration. Alternatively, the amino acid can be a derivative of alanyl, valinyl, leucinyl, isoleuccinyl, prolinyl, phenylalaninyl, tryptophanyl, methioninyl, glycinyl, serinyl, threoninyl, cysteinyl, tyrosinyl, asparaginyl, glutaminyl, aspartoyl, glutaroyl, lysinyl, argininyl, histidinyl, β-alanyl, β-valinyl, β-leucinyl, β-isoleuccinyl, β-prolinyl, β-phenylalaninyl, β-tryptophanyl, β-methioninyl, β-glycinyl, β-serinyl, β-threoninyl, β-cysteinyl, β-tyrosinyl, β-asparaginyl, β-glutaminyl, β-aspartoyl, β-glutaroyl, β-lysinyl, β-argininyl or β-histidinyl.

As used herein, the terms "substantially free of" and "substantially in the absence of" refer to a nucleoside composition that includes at least 85 or 90% by weight, preferably at least 95% or 98% by weight, and even more preferably at least 99% or 100% by weight, of the designated enantiomer of that nucleoside. In a preferred embodiment, the compounds listed in the methods and compounds of this invention are substantially free of enantiomers other than for the one designated.

Similarly, the term "isolated" refers to a nucleoside composition that includes at least 85% or 90% by weight, preferably 95% or98% y weight, and even more preferably 99% or 100% by weight, of the nucleoside.

The term "host", as used herein, refers to a unicellular or multicellular organism in which the virus can replicate, including cell lines and animals, and preferably a human. Alternatively, the host can be carrying a part of the coronavirus, togavirus and/or picornavirus genome, whose replication or function can be altered by the compounds of the present invention. The term host specifically refers to infected cells, cells transfected with all or part of the coronavirus, togavirus and/or picornavirus genome and animals, in particular, primates (including chimpanzees) and humans. In most animal applications of the present invention, the host is a human patient. Veterinary applications, in certain indications, however, are clearly anticipated by the present invention such as in chimpanzees.

The term "pharmaceutically acceptable salt or prodrug" is used throughout the specification to describe any pharmaceutically acceptable form (ester, phosphate ester, salt of an ester or a related group) of a nucleoside compound, which, upon administration to a patient, provides the nucleoside compound. Pharmaceutically acceptable salts

include those derived from pharmaceutically acceptable inorganic or organic bases and acids. Suitable salts include those derived from alkali metals such as potassium and sodium, alkaline earth metals such as calcium and magnesium, among numerous other acids well known in the pharmaceutical art. Pharmaceutically acceptable prodrugs refer to a compound that is metabolized, for example, hydrolyzed or oxidized, in the host to form the compound of the present invention. Typical examples of prodrugs include compounds that have biologically labile protecting groups on a functional moiety of the active compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, dephosphorylated to produce the active compound. The compounds of this invention possess antiviral activity against coronavirus, togavirus and/or picornavirus or are metabolized to a compound that exhibits such activity.

III. Nucleotide Prodrug Formulations

Any of the nucleosides described herein can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside. A number of nucleotide prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono-, di- or triphosphate of the nucleoside reduces polarity and allows passage into cells. Examples of substituent groups that can replace one or more hydrogens on the phosphate moiety are alkyl, aryl, steroids, carbohydrates, including sugars, 1,2-diacylglycerol and alcohols. Many are described in R. Jones and N. Bischoferger, *Antiviral Research*, 1995, 27:1-17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect.

In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compound as a pharmaceutically acceptable salt may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids, which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate,

benzoate, ascorate, α-ketoglutarate, and α-glycerophosphate. Suitable inorganic salts may also be formed, including, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

The active nucleoside can also be provided as a 5'-phosphoether lipid or a 5'-ether lipid, as disclosed in the following references, which are incorporated by reference herein: Kucera, L.S., N. Iyer, E. Leake, A. Raen, Modest E.K., D.L.W., and C. Piantadosi. 1990. "Novel membrane-interactive ether lipid analogs that inhibit infectious HIV-1 production and induce defective virus formation." *AIDS Res. Hum. Retro Viruses*. 6:491-501; Piantadosi, C., J. Marasco C.J., S.L. Morris-Natschke, K.L. Meyer, F. Gumus, J.R. Surles, K.S. Ishaq, L.S. Kucera, N. Iyer, C.A. Wallen, S. Piantadosi, and E.J. Modest. 1991. "Synthesis and evaluation of novel ether lipid nucleoside conjugates for anti-HIV activity." *J. Med. Chem.* 34:1408.1414; Hosteller, K.Y., D.D. Richman, D.A. Carson, L.M. Stuhmiller, G.M. T. van Wijk, and H. van den Bosch., 1992. "Greatly enhanced inhiition of human immunodeficiency virus type 1 replication in CEM and HT4-6C cells by 3'-deoxythymidine diphosphate dimyristoylglycerol, a lipid prodrug of 3-deoxythymidine." *Antimicro. Agents Chemother.* 36:2025.2029; Hosetler, K.Y., L.M. Stuhmiller, H.. Lenting, H. van den Bosch, and D.D. Richman, 1990. "Synthesis and antiretroviral activity of phospholipid analogs of azidothymidine and other antiviral nucleosides." *J. Biol. Chem.* 265:61127.

Nonlimiting examples of U.S. patents that disclose suitable lipophilic substituents that can be covalently incorporated into the nucleoside, preferably at the 5'-OH position of the nucleoside or lipophilic preparations, include U.S. Patent Nos. 5,149,794 (Sep. 22, 1992, Yatvin *et al.*); 5,194,654 (Mar. 16, 1993, Hostetler *et al.*, 5,223,263 (June 29, 1993, Hostetler *et al.*); 5,256,641 (Oct. 26, 1993, Yatvin *et al.*); 5,411,947 (May 2, 1995, Hostetler *et al.*); 5,463,092 (Oct. 31, 1995, Hostetler *et al.*); 5,543,389 (Aug. 6, 1996, Yatvin *et al.*); 5,543,390 (Aug. 6, 1996, Yatvin *et al.*); 5,543,391 (Aug. 6, 1996, Yatvin *et al.*); and 5,554,728 (Sep. 10, 1996; Basava *et al.*), all of which are incorporated herein by reference. Foreign patent applications that disclose lipophilic substituents that can be

attached to the nucleosides of the present invention, or lipophilic preparations, include WO 89/02733, W0 90/00555, W0 91/16920, W0 91/18914, W0 93/00910, W0 94/26273, W0 96/15132, EP 0 350 287, EP 93917054.4, and W0 91/19721.

IV. Combination and Alternation Therapy

Drug-resistant variants of coronavirus, togavirus and/or picornavirus may emerge after prolonged treatment with an antiviral agent. Drug resistance most typically occurs by mutation of a gene that encodes for an enzyme used in viral replication. The efficacy of a drug against the viral infection can be prolonged, augmented, or restored by administering the compound in combination or alternation with a second, and perhaps third, antiviral compound that induces a different mutation from that caused by the principle drug. Alternatively, the pharmacokinetics, biodistribution or other parameter of the drug can be altered by such combination or alternation therapy. In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus.

Any of the viral treatments described in the Background of the Invention can be used in combination or alternation with the compounds described in this specification. Nonlimiting examples include:

(1) Interferon

A number of patents disclose anti-viral treatments, using interferon-based therapies. For example, U.S. Patent No. 5,928,636 to Alber et al. discloses the combination therapy of interleukin-12 and interferon alpha for the treatment of infectious diseases. U.S. Patent No. 5,849,696 to Chretien et al. discloses the use of thymosins, alone or in combination with interferon. U.S. Patent No. 5,830,455 to Valtuena et al. discloses a combination therapy employing interferon and a free radical scavenger. U.S. Patent No. 5,738,845 to Imakawa discloses the use of human interferon tau proteins. Other interferon-based treatments are disclosed, for example, in U.S. Patent No. 5,676,942 to Testa et al., U.S. Patent No. 5,372,808 to Blatt et al., and U.S. Patent No. 5,849,696. A number of patents also disclose pegylated forms of interferon, such as U.S. Patent Nos. 5,747,646, 5,792,834 and 5,834,594 to Hoffmann-La Roche Inc; PCT

Publication No. WO 99/32139 and WO 99/32140 to Enzon; WO 95/13090 and US Patent Nos. 5,738,846 and 5,711,944 to Schering; and U.S. Patent No. 5,908,621 to Glue et al..

Interferon alpha-2a and interferon alpha-2b are currently approved as monotherapy. For example, ROFERON®-A (Roche) is the recombinant form of interferon alpha-2a. Pegasys® (Roche) is the pegylated (i.e. polyethylene glycol modified) form of interferon alpha-2a. INTRON®A (Schering Corporation) is the recombinant form of Interferon alpha-2b, and PEG-INTRON® (Schering Corporation) is the pegylated form of interferon alpha-2b.

Other forms of interferon alpha, as well as interferon beta, gamma, tau and omega are currently in clinical development. For example, INFERGEN (interferon alphacon-1) by InterMune, OMNIFERON (natural interferon) by Viragen, ALBUFERON by Human Genome Sciences, REBIF (interferon beta-1a) by Ares-Serono, Omega Interferon by BioMedicine, Oral Interferon Alpha by Amarillo Biosciences, and interferon gamma, interferon tau, and interferon gamma- 1b by InterMune are in development.

Combination of Interferon and Ribavirin

Combination therapy with an alpha interferon and ribavirin is a common anti-viral therapy. The combination of interferon and ribavirin has been reported to be effective in the treatment of interferon naïve patients (for example, Battaglia, A.M. et al., Ann. Pharmacother. 34:487-494, 2000), as well as for treatment of patients when histological disease is present (Berenguer, M. et al. Antivir. Ther. 3(Suppl. 3):125-136, 1998). Studies have show that more patients respond to pegylated interferon-alpha/ribavirin combination therapy than to combination therapy with unpegylated interferon alpha. However, as with monotherapy, significant side effects develop during combination therapy, including hemolysis, flu-like symptoms, anemia, and fatigue. (for example, Gary L. Davis. Gastroenterology 118:S104-S114, 2000).

Combination therapy with PEG-INTRON® (peginterferon alpha-2b) and REBETOL® (Ribavirin, USP) capsules is available from Schering Corporation. REBETOL® (Schering Corporation) has also been approved in combination with INTRON® A (Interferon alpha-2b, recombinant, Schering Corporation). Roche's

Pegasys® (pegylated interferon alpha-2a) and COPEGUS® (ribavirin) are also approved for the treatment of HCV.

PCT Publication Nos. WO 99/59621, WO 00/37110, WO 01/81359, WO 02/32414 and WO 03/024461 by Schering Corporation disclose the use of pegylated interferon alpha and ribavirin combination therapy. PCT Publication Nos. WO 99/15194, WO 99/64016, and WO 00/24355 by Hoffmann-La Roche Inc also disclose the use of pegylated interferon alpha and ribavirin combination.

(3) Substrate-based NS3 protease inhibitors (for example, Attwood et al., Antiviral peptide derivatives, PCT WO 98/22496, 1998; Attwood et al., Antiviral Chemistry and Chemotherapy 1999, 10, 259-273; Attwood et al., Preparation and use of amino acid derivatives as anti-viral agents, German Patent Pub. DE 19914474; Tung et al. Inhibitors of serine proteases, particularly hepatitis C virus NS3 protease, PCT WO 98/17679), including alphaketoamides and hydrazinoureas, and inhibitors that terminate in an electrophile such as a boronic acid or phosphonate (Llinas-Brunet et al, Hepatitis C inhibitor peptide analogues, PCT WO 99/07734).

(4) Non-substrate-based inhibitors, for example, 2,4,6-trihydroxy-3-nitro-benzamide derivatives (for example, Sudo K. et al., Biochemical and Biophysical Research Communications, 1997, 238, 643-647; Sudo K. et al. Antiviral Chemistry and Chemotherapy, 1998, 9, 186), including RD3-4082 and RD3-4078, the former substituted on the amide with a 14 carbon chain and the latter processing a para-phenoxyphenyl group;

(5) Thiazolidine derivatives which show relevant inhibition in a reverse-phase HPLC assay (for example Sudo K. et al., Antiviral Research, 1996, 32, 9-18), especially compound RD-1-6250, possessing a fused cinnamoyl moiety substituted with a long alkyl chain, RD4 6205 and RD4 6193;

(6) Thiazolidines and benzanilides (for example Kakiuchi N. et al. J. EBS Letters 421, 217-220; and Takeshita N. et al. Analytical Biochemistry, 1997, 247, 242-246);

(7) A phenanthrenequinone possessing activity against protease in a SDS-PAGE and autoradiography assay isolated from the fermentation culture broth of Streptomyces sp., for example, Sch 68631 (for example, Chu M. et al., Tetrahedron Letters, 1996, 37, 7229-7232), and Sch 351633, isolated from the fungus Penicillium griscofuluum, which demonstrates activity in a scintillation proximity assay (for example, Chu M. et al., Bioorganic and Medicinal Chemistry Letters 9, 1949-1952);

(8) Selective NS3 inhibitors, for example, those based on the macromolecule elgin c, isolated from leech (for example, Qasim M.A. et al., Biochemistry, 1997, 36, 1598-1607);

(9) Helicase inhibitors (for example Diana G.D. et al., Compounds, compositions and methods for treatment of hepatitis C, U.S. Pat. No. 5,633,358; Diana G.D. et al., Piperidine derivatives, pharmaceutical compositions thereof and their use in the treatment of hepatitis C, PCT WO 97/36554);

(10) Polymerase inhibitors for example nucleotide analogues, gliotoxin (for example, Ferrari R. et al. Journal of Virology, 1999, 73, 1649-1654), and the natural product cerulenin (for example, Lohmann V. et al., Virology, 1998, 249, 108-118);

(11) Antisense phosphorothioate oligodeoxynucleotides (S-ODN) complementary to sequence stretches in the 5' non-coding region (NCR) of the virus (for example, Alt M. et al., Hepatology, 1995, 22, 707-717), or nucleotides comprising the 3' end of the NCR and/or nucleotides located in the core coding region of the viral RNA (for example, Alt M. et al., Archives of Virology, 1997, 142, 589-599; Galderisi U. et al., Journal of Cellular Physiology, 1999, 181, 251-257).

(12) Inhibitors of IRES-dependent translation (for example, Ikeda N et al., Agent for the prevention and treatment of hepatitis C, Japanese Patent Pub. JP-08268890; Kai Y. et al. Prevention and treatment of viral diseases, Japanese Patent Pub. JP-10101591).

(13) Nuclease-resistant ribozymes (for example Maccjak, D. J. et al., Hepatology 1999, 30, abstract 995).

(14) Nucleoside analogs have also been developed for the treatment of viral infections. Examples include the following.

Idenix Pharmaceuticals, Ltd. discloses branched nucleosides, and their use in the treatment of HCV and flaviviruses and pestiviruses in US Patent Publication No. 2003/0050229 A1 and US Patent Publication No. 2003/0060400 A1, which correspond to International Publication Nos. WO 01/90121 and WO 01/92282. A method for the treatment of hepatitis C infection (and flaviviruses and pestiviruses) in humans and other host animals is disclosed in the Idenix publications that includes administering an effective amount of a biologically active 1', 2 ', 3' or 4'-branched β-D or β-L nucleosides or a pharmaceutically acceptable salt or prodrug thereof, administered either alone or in combination, optionally in a pharmaceutically acceptable carrier. See also U.S. Patent Publication Nos. 2004/0006002 and 2004/0006007 as well as WO 03/026589 and WO 03/026675. Idenix Pharmaceuticals, Ltd. also discloses in US Patent Publication No. 2004/0077587 pharmaceutically acceptable branched nucleoside prodrugs, and their use in the treatment of HCV and flaviviruses and pestiviruses in prodrugs. See also PCT Publication Nos. WO 04/002422, WO 04/002999, and WO 04/003000.

Emory University and the University of Georgia Research Foundation, Inc. (UGARF) discloses the use of 2'-fluoronucleosides in US Patent No. 6,348,587. See also International Patent Publication WO 99/43691.

BioChem Pharma Inc. (now Shire Biochem, Inc.) discloses the use of various 1,3-dioxolane nucleosides in International Publication No. WO 01/32153 (PCT/CA00/01316; filed November 3, 2000).

BioChem Pharma Inc. (now Shire Biochem, Inc.) also disclose s various other 2'-halo, 2'-hydroxy and 2'-alkoxy nucleosides in International Publication No. WO 01/60315 (PCT/CA01/00197; filed February 19, 2001).

ICN Pharmaceuticals, Inc. discloses various nucleoside analogs that are useful in modulating immune response in US Patent Nos. 6,495,677 and 6,573,248. See also WO 98/16184, WO 01/68663, and WO 02/03997.

US Patent Publication Nos. 2003/083307 A1 and US 2003/008841 A1, and the corresponding International Patent Publication Nos. WO 02/18404 (PCT/EP01/09633; published August 21, 2001); WO 02/100415 and WO 02/094289, filed by F. Hoffmann-

La Roche AG discloses various nucleoside analogs for the inhibition of viral RNA replication.

Pharmasset Limited discloses various nucleosides and antimetabolites for the treatment of a variety of viruses, in WO 02/32920, WO 01/79246, WO 02/48165, WO 03/068162, WO 03/068164 and 2004/013298.

Merck & Co., Inc. and Isis Pharmaceuticals disclose in US Patent Publication No. 2002/0147160 and the corresponding International Patent Publication Nos. WO 02/057425 (PCT/US02/01531; filed January 18, 2002) and WO 02/057287 (PCT/US02/03086; filed January 18, 2002) various nucleosides, and in particular several pyrrolopyrimidine nucleosides, for the treatment of viruses whose replication is dependent upon RNA-dependent RNA polymerase. See also WO 03/068244, WO 2004/003138, WO 2004/007512, and WO 2004/009020.

US Patent Publication No. 2003/028013 A1 as well as International Patent Publication Nos. WO 03/051899, WO 03/061576, WO 03/062255 WO 03/062256, WO 03/062257, and WO 03/061385, filed by Ribapharm, also are directed to the use of certain nucleoside analogs to treat viral infections.

(15) Miscellaneous compounds including, for example, 1-amino-alkylcyclohexanes (for example, U.S. Patent No. 6,034,134 to Gold et al.), alkyl lipids (for example, U.S. Pat. No. 5,922,757 to Chojkier et al.), vitamin E and other antioxidants (for example, U.S. Pat. No. 5,922,757 to Chojkier et al.), squalene, amantadine, bile acids (for example, U.S. Pat. No. 5,846,964 to Ozeki et al.), N-(phosphonoacetyl)-L-aspartic acid (for example, U.S. Pat. No. 5,830,905 to Diana et al.), benzenedicarboxamides (for example, U.S. Pat. No. 5,633,388 to Diana et al.), polyadenylic acid derivatives (for example, U.S. Pat. No. 5,496,546 to Wang et al.), 2',3'-dideoxyinosine (for example, U.S. Pat. No. 5,026,687 to Yarchoan et al.), and benzimidazoles for example, (U.S. Pat. No. 5,891,874 to Colacino et al.).

(16) Other compounds currently in clinical development include, for example: Interleukin-10 by Schering-Plough, IP-501 by Interneuron, Merimebodib VX-497 by Vertex, AMANTADINE (Symmetrel) by Endo Labs Solvay, HEPTAZYME by RPI, IDN-6556 by Idun Pharma., XTL-002 by XTL., HCV/MF59 by Chiron, CIVACIR by

NABI, LEVOVIRIN by ICN, VIRAMIDINE by ICN, ZADAXIN (thymosin alfa-1) by Sci Clone, CEPLENE (histamine dihydrochloride) by Maxim, VX 950 / LY 570310 by Vertex/Eli Lilly, ISIS 14803 by Isis Pharmaceutical/Elan, IDN-6556 by Idun Pharmaceuticals, Inc. and JTK 003 by AKROS Pharma.

V. Pharmaceutical Compositions

Hosts, including humans, infected with a coronavirus, togavirus and/or picornavirus or another organism replicating through a RNA-dependent RNA viral polymerase, can be treated by administering to the patient an effective amount of the active compound or a pharmaceutically acceptable prodrug or salt thereof in the presence of a pharmaceutically acceptable carrier or diluent. The active materials can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, sucutaneously, or topically, in liquid or solid form.

A preferred dose of the compound for a coronavirus, togavirus and/or picornavirus will be in the range from about 1 to 50 mg/kg, preferably 1 to 20 mg/kg, of body weight per day, more generally 0.1 to about 100 mg per kilogram body weight of the recipient per day. The effective dosage range of the pharmaceutically acceptable salts and prodrugs can be calculated based on the weight of the parent nucleoside to be delivered. If the salt or prodrug exhibits activity in itself, the effective dosage can be estimated as above using the weight of the salt or prodrug, or by other means known to those skilled in the art.

The compound is conveniently administered in unit any suitable dosage form, including but not limited to one containing 7 to 3000 mg, preferably 70 to 1400 mg of active ingredient per unit dosage form. An oral dosage of 50-1000 mg is usually convenient.

Ideally the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.2 to 70 μM, preferably about 1.0 to 10 μM. This may be achieved, for example, by the intravenous injection of a 0.1 to 5% solution of the active ingredient, optionally in saline, or administered as a bolus of the active ingredient.

The concentration of active compound in the drug composition will depend on absorption, inactivation and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need. and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time.

A. preferred mode of administration of the active compound is oral. Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible inding agents, and/or adjuvant materials can e included as part of the composition.

The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

The compound can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The compound or a pharmaceutically acceptable prodrug or salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, anti-inflammatories, or other antivirals, including other nucleoside compounds. Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antiacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposale syringes or multiple dose vials made of glass or plastic.

If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PS).

In a preferred embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. biodegradale, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation.

Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antiodies to viral antigens) are also preferred as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811 (which is incorporated herein by reference in its entirety). For example, liposome formulations may be prepared by dissolving appropriate lipid(s) (such as stearoyl phosphatidyl ethanolamine, stearoyl phosphatidyl choline, arachadoyl phosphatidyl choline, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound or its monophosphate, diphosphate, and/or triphosphate derivatives is then introduced into the container. The

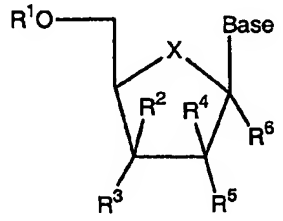
container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

VI. Processes for the Preparation of Active Compounds

The nucleosides of the present invention can be synthesized by any means known in the art. In particular, the synthesis of the present nucleosides can be achieved by either alkylating the appropriately modified sugar, followed by glycosylation or glycosylation followed by alkylation of the nucleoside, though preferably alkylating the appropriately modified sugar, followed by glycosylation. The following non-limiting embodiments illustrate some general methodology to obtain the nucleosides of the present invention.

A. General Synthesis of 1'-C-branched Nucleosides

A 1'-C branched ribonucleoside of the following structure, for example:



(I)

or a pharmaceutically acceptable salt, ester, salt of an ester, prodrug, or salt of a prodrug, thereof, wherein:

R^1 is H, phosphate or phosphonate (including mono-, di-, or triphosphate or a stabilized phosphate prodrug); optionally substituted acyl (including lower acyl); optionally substituted alkyl (including lower alkyl); optionally substituted sulfonate ester including alkyl or arylalkyl sulfonyl such as methanesulfonyl; optionally substituted aryl; optionally substituted benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of an aryl given herein; optionally substituted arylsulfonyl; a lipid,

including a phospholipid; an amino acid derivative; a carbohydrate; a peptide; cholesterol; or other pharmaceutically acceptable leaving group that when administered *in vivo*, provides a compound wherein R^1 is independently H or phosphate;

each R^2 and R^4 independently is H, OH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, halo (F, Cl, Br, or I), NO_2, NH_2, N_3, CH_2N_3, CH_2NH_2, CN, CH_2CN, CH_2N_3, CH_2NHCH_3, $CH_2N(CH_3)_2$, CH_2OH, halogenated alkyl, alkoxy, CF_3, $C(A)_3$, 2-Br-ethyl, CH_2F, CH_2Cl, CH_2CF_3, CF_2CF_3, $CH_2(A)$, $C(A)_2C(A)_3$, SCN, OCN, NCO, haloalkenyl, Br-vinyl, haloalkynyl; $-(CH_2)_mC(O)OR^{13}$, $-(CH_2)_mC(O)SR^{13}$; -O(alkenyl), $-(CH_2)_mNHR^{13}$, $-(CH_2)_mN(R^{13})_2$, $-(CH_2)_mC(O)NHR^{13}$, $-(CH_2)_mC(O)N(R^{13})_2$, $-C(O)OR^{13}$, $-O(R^{13})$, an optionally substituted carbocycle, an optionally substituted heterocycle, an optionally substituted heteroaryl (preferably a heteroaromatic ring having one or more O, S and/or N atoms), or C_{3-7} cycloalkylamino;

each R^3, R^5 and R^6 independently is H, OH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, halo (F, Cl, Br, or I), NO_2, NH_2, N_3, CH_2N_3, CH_2NH_2, CN, CH_2CN, CH_2N_3, CH_2NHCH_3, $CH_2N(CH_3)_2$, CH_2OH, halogenated alkyl, alkoxy, CF_3, $C(A)_3$, 2-Br-ethyl, CH_2F, CH_2Cl, CH_2CF_3, CF_2CF_3, $CH_2(A)$, $C(A)_2C(A)_3$, SCN, OCN, NCO, haloalkenyl, Br-vinyl, haloalkynyl; $-(CH_2)_mC(O)OR^{13}$, $-(CH_2)_mC(O)SR^{13}$; -O(alkenyl), $-(CH_2)_mNHR^{13}$, $-(CH_2)_mN(R^{13})_2$, $-(CH_2)_mC(O)NHR^{13}$, $-(CH_2)_mC(O)N(R^{13})_2$, $-C(O)OR^{13}$, $-O(R^{13})$, an optionally substituted carbocycle (preferably a 3-7 membered carbocyclic ring such as, for example, a C_{3-7} cycloalkylamino), an optionally substituted heterocycle (preferably a 3-7 membered heterocyclic ring having one or more O, S and/or N), an optionally substituted heteroaryl (preferably a heteroaromatic ring having one or more O, S and/or N atoms), a C_{3-7} cycloalkylamino, CF_3, mercapto, optionally substituted C_{1-4} alkyl, C_{1-12} alkoxy, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{2-6} alkenyloxy, C_{1-4} alkylthio, C_{1-8} alkylcarbonyloxy, aryloxycarbonyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, Br-vinyl, -C(O)O(alkyl), O-phosphate or O-phosphonate (including mono-, di-, or triphosphate or a stabilized phosphate prodrug); O-acyl (including lower acyl); O-alkyl (including lower alkyl); O-sulfonate ester including O-alkyl or O-

arylalkyl sulfonyl including O-methanesulfonyl; O-aryl; O-benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of an aryl given herein; -OC(O)O-aryl; -OC(O)O-aralkyl; -S(acyl); -S(alkyl); -S(alkenyl); optionally substituted O-arylsulfonyl; an O-linked lipid, including an O-phospholipid; an O-linked amino acid; an O-linked carbohydrate; an O-linked peptide; O-linked cholesterol; or other O-linked pharmaceutically acceptable leaving group that when administered *in vivo*, provides a compound wherein the requisite R^3, R^5 or R^6 is independently OH or O-phosphate;

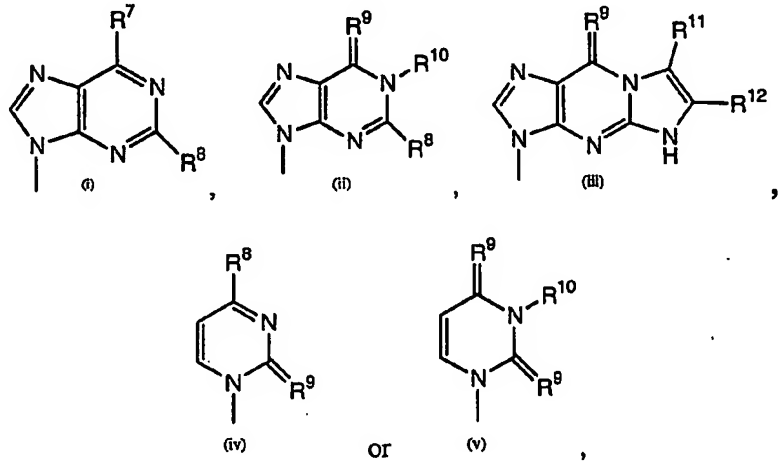
X is O, S, SO_2, CH_2, or CHOH;

m is 0, 1 or 2;

R^{13} is H, alkyl, alkenyl, alkynyl, acyl, aryl or aralkyl;

A is H, OH, C_{1-4} alkyl, halo, azido, cyano, C_{2-6} alkenyl, C_{2-6} alkynyl, Br-vinyl, 2-Br-ethyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), CF_3, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, or -N(acyl)$_2$; and

Base is as defined in the specification, including but not limited to:



wherein:

Each R^7, R^8, R^{10}, R^{11} and R^{12} independently is H, NH_2, SH, CF_3, halo, NO_2, N_3, optionally substituted alkyl, optionally substituted alkenyl, optionally

substituted alkynyl, optionally substituted aryl (preferably optionally substituted phenyl), -NH-cycloalkyl, -NH-cycloalkenyl, -NH-heterocycle, -NH-heteroaryl, -O-cycloalkyl, -O-cycloalkenyl, -O-heterocycle, -O-heteroaryl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{3-6} cycloalkylamino, C_{1-4} alkyl-C(=O)OH, C_{1-4} alkyl-C(=O)O-aryl (preferably C_{1-4} alkyl-C(=O)O-phenyl), C_{1-4} alkyl-C(=O)O-heterocycle, C_{1-4} alkyl-C(=O)O-heteroaryl, or C_{1-4} alkoxy;

R^9 is O or S; and

all tautomeric, enantiomeric and stereoisomeric forms thereof.

Modification from the Lactone

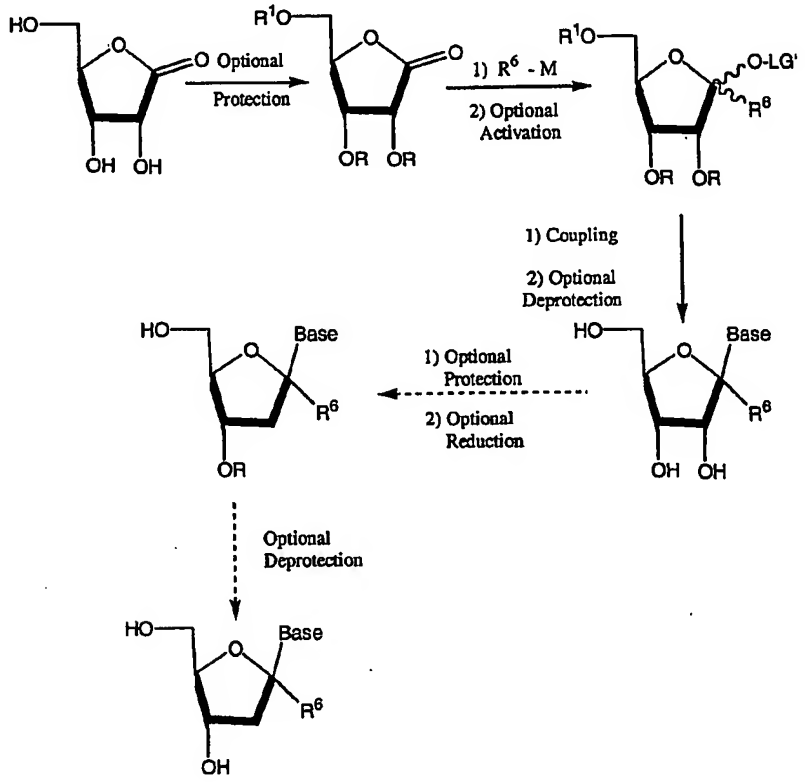
The key starting material for this process is an appropriately substituted lactone. The lactone may be purchased or can be prepared by any known means including standard epimerization, substitution and cyclization techniques. The lactone optionally can be protected with a suitable protecting group, preferably with an acyl or silyl group, by methods well known to those skilled in the art, as taught by Greene et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991. The protected lactone can then be coupled with a suitable coupling agent, such as an organometallic carbon nucleophile like a Grignard reagent, an organolithium, lithium dialkylcopper or R^6-$SiMe_3$ in TAF with the appropriate non-protic solvent at a suitable temperature, to give the 1'-alkylated sugar.

The optionally activated sugar can then be coupled to the base by methods well known to those skilled in the art, as taught by Townsend, Chemistry of Nuceleotides, Plenum Press, 1994. For example, an acylated sugar can be coupled to a silylated base with a Lewis acid such as tin tetrachloride, titanium tetrachloride, or trimethylsilyltriflate in the appropriate solvent at a suitable temperature.

Subsequently, the nucleoside can be deprotected by methods well known to those skilled in the art, as taught by Greene et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

In a particular embodiment, the 1'-C-branched ribonucleoside is desired. The synthesis of a ribonucleoside is shown in Scheme 1. Alternatively, dexoyribonucleoside is desired. To obtain these nucleosides, the formed ribonucleoside an optionally be protected by methods well known to those skilled in the art, as taught by Greene et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, and then the 2'-OH can be reduced with a suitable reducing agent. Optionally, the 2'-OH can be activated to facilitate reduction as, for example, via the Barton reduction.

Scheme 1



Alternative Method for the Preparation of 1'-C-branched Nucleosides

The key starting material for this process is an appropriately substituted hexose. The hexose can be purchased or can be prepared by any known means including standard epimerization (as, for example, via alkaline treatment), substitution and coupling techniques. The hexose can be protected selectively to give the appropriate hexa-

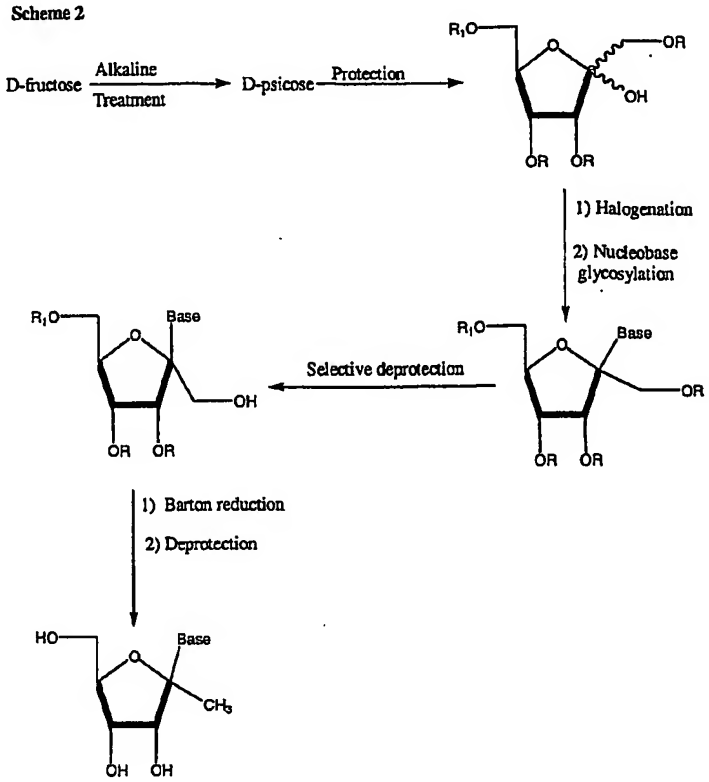
furanose, as taught by Townsend, Chemistry of Nucleosides and Nucleotides, Plenum Press, 1994.

The 1'-OH optionally can be activated to a suitable leaving group such as an acyl group or a halogen via acylation or halogenation, respectively. The optionally activated sugar can then be coupled to the base by methods well known to those skilled in the art, as taught by Townsend, Chemistry of Nucleosides and Nucleotides, Plenum Press, 1994. For example, an acylated sugar can be coupled to a silylated base with a Lewis acid, such as tin tetrachloride, titanium tetrachloride, or trimethylsilyltriflate in an appropriate solvent at a suitable temperature. Alternatively, a halo-sugar can be coupled to a silylated base in the presence of trimethylsilyltriflate.

The 1'-CH_2-OH, if protected, selectively can be deprotected by methods well known in the art. The resultant primary hydroxyl can be reduced to give the methyl, using a suitable reducing agent. Alternatively, the hydroxyl can be activated prior to reduction to facilitate the reaction, i.e., via the Barton reduction. In an alternate embodiment, the primary hydroxyl can be oxidized to the aldehyde, then coupled with a carbon nucleophile such as a Grignard reagent, an organolithium, lithium dialkylcopper or R^6-$SiMe_3$ in TAF with an appropriate non-protic solvent at a suitable temperature.

In a particular embodiment, the 1'-C-branched ribonucleoside is desired. The synthesis of a ribonucleoside is shown in Scheme 2. Alternatively, deoxyribonucleoside is desired. To obtain these nucleosides, the formed ribonucleoside optionally can be protected by methods well known to those skilled in the art, as taught by Greene et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, and then the 2'-OH can be reduced with a suitable reducing agent. Optionally, the 2'-OH can be activated to facilitate reduction as, for example, via the Barton reduction.

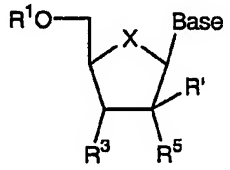
Scheme 2



In addition, the L-enantiomers corresponding to the compounds of the invention can be prepared following the same general methods (1 or 2), beginning with the corresponding L-sugar or nucleoside L-enantiomer as the starting material.

General Synthesis of 2'-C-branched Nucleosides

A 2'-C-branched ribonucleoside of the following structure as an example:



(II)

wherein

R^1, R^3, R^5, and R' are all as defined above;

X is as defined above;

Base is as defined in the specification; or

a pharmaceutically acceptable salt or prodrug thereof; and

all tautomeric, enantiomeric and stereoisomeric forms thereof.

1. Glycosylation of the nucleoase with an appropriately modified sugar

The key starting material for this process is an appropriately substituted sugar with a 2'-OH and 2'-H, with an appropriate leaving group (LG), such as an acyl or halogen group, for example. The sugar can be purchased or can be prepared by any known means including standard epimerization, substitution, oxidation and/or reduction techniques. The substituted sugar can then be oxidized with an appropriate oxidizing agent in a compatible solvent at a suitable temperature to yield the 2'-modified sugar. Possible oxidizing agents are Jones' reagent (a mixture of chromic and sulfuric acids), Collins' reagent (dipyridine Cr(VI)oxide), Corey's reagent (pyridinium chlorochromate), pyridinium dichromate, acid dichromate, potassium permanganate, MnO_2, ruthenium tetroxide, phase transfer catalysts such as chromic acid or permanganate supported on a polymer, Cl_2-pyridine, H_2O_2-ammonium molydate, $NarO_2$-CAN, NaOCl in HOAc, copper chromate, copper oxide, Raney nickel, palladium acetate, Meerwin-Pondorf-Verley reagent (aluminum *t*-utoxide with another ketone) and *N*-bromosuccinimide.

Then coupling of an organometallic carbon nucleophile such as a Grignard reagent, an organolithium, lithium dialkylcopper or R^6-$SiMe_3$ in TAF with the ketone and an appropriate non-protic solvent at a suitable temperature, yields the 2'-alkylated sugar. The alkylated sugar optionally can be protected with a suitable protecting group, preferably with an acyl or silyl group, by methods well known to those skilled in the art, as taught by Greene et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

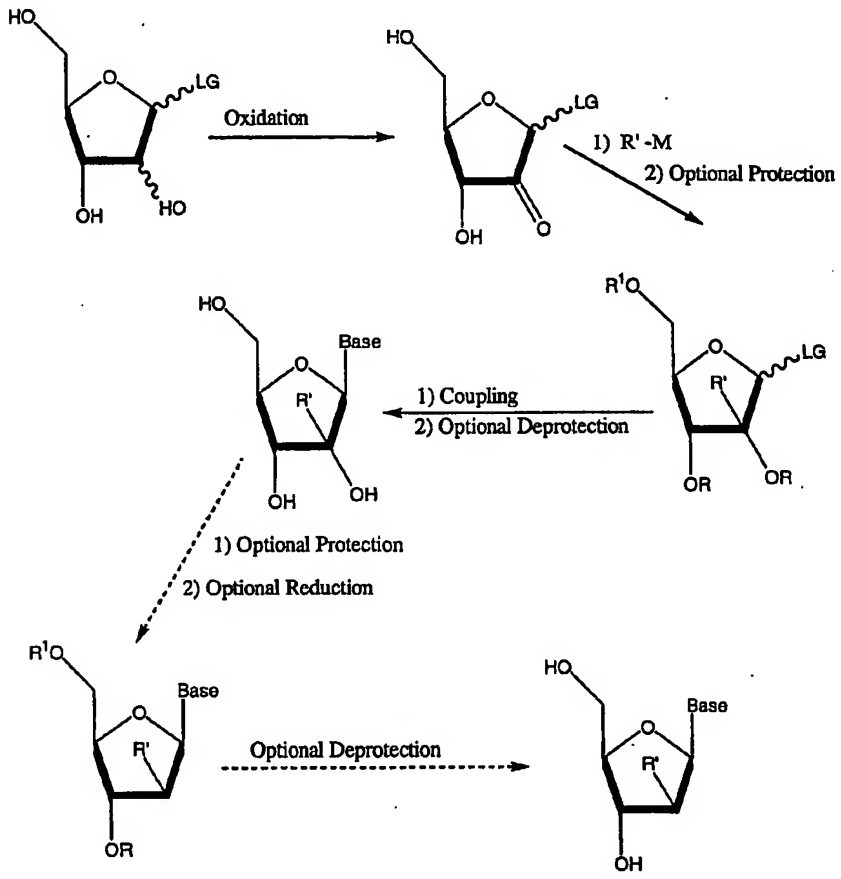
The optionally protected sugar can then be coupled to the base by methods well known to those skilled in the art, as taught by Townsend, Chemistry of Nucleosides and Nucleotides, Plenum Press, 1994. For example, an acylated sugar can be coupled to a silylated base with a Lewis acid, such as tin tetrachloride, titanium tetrachloride, or

trimethylsilyltriflate in an appropriate solvent at a suitable temperature. Alternatively, a halo-sugar can e coupled to a silylated base in the presence of trimethylsilyltriflate.

Subsequently, the nucleoside can be deprotected by methods well known to those skilled in the art, as by Greene et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

In a particular embodiment, the 2'-C-branched ribonucleoside is desired, the synthesis of which is shown in Scheme 3. Alternatively, a deoxyribonucleoside is desired. To obtain these nucleosides, the formed ribonucleoside can optionally be protected by methods well known to those skilled in the art, as by Greene et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, and then the 2'-OH can e reduced with a suitable reducing agent. Optionally, the 2'-OH can be activated to facilitate reduction, such as, for example, by the Barton reduction.

Scheme 3



2. Modification of a pre-formed nucleoside

The key starting material for this process is an appropriately substituted nucleoside with a 2'-OH and 2'-H. The nucleoside can be purchased or can be prepared by any known means including standard coupling techniques. The nucleoside optionally can be protected with suitable protecting groups, preferably with acyl or silyl groups, by methods well known to those skilled in the art, as by Greene et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

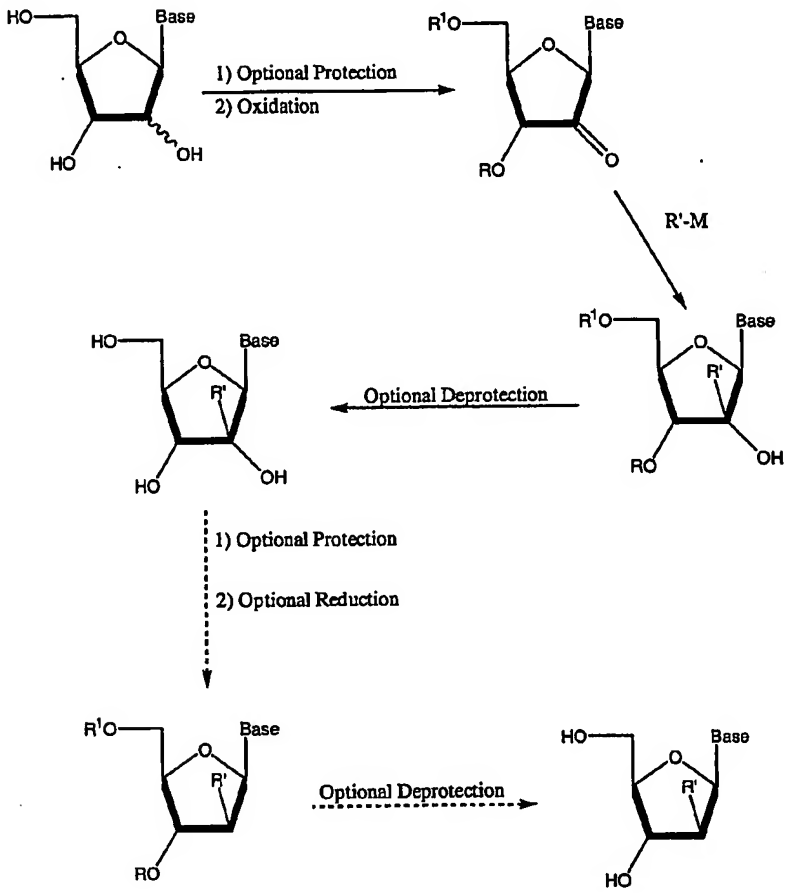
The appropriately protected nucleoside then can be oxidized with an appropriate oxidizing agent in a compatible solvent at a suitable temperature to yield the 2'-modified sugar. Possible oxidizing agents include Jones' reagent (a mixture of chromic and

sulfuric acids), Collins' reagent (dipyridine Cr(VI)oxide), Corey's reagent (pyridinium chlorochromate), pyridinium dichromate, acid dichromate, potassium permanganate, MnO_2, ruthenium tetroxide, phase transfer catalysts such as chromic acid or permanganate supported on a polymer, Cl_2-pyridine, H_2O_2-ammonium molydate, $NarO_2$-CAN, NaOCl in HOAc, copper chromate, copper oxide, Raney nickel, palladium acetate, Meerwin-Pondorf-Verley reagent (aluminum *t*-butoxide with another ketone) and *N*-bromosuccinimide.

Subsequently, the nucleoside can e deprotected y methods well known to those skilled in the art, as by Greene et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

In a particular embodiment, a 2'-C-branched ribonucleoside is desired, the synthesis of which is shown in Scheme 4. Alternatively, the deoxyribonucleoside may be desired. To obtain these nucleosides, the formed ribonucleoside optionally may be protected by methods well known to those skilled in the art, as by Greene et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, and then the 2'-OH can be reduced with a suitable reducing agent. Optionally, the 2'-OH can be activated to facilitate reduction such as, for example, by the Barton reduction.

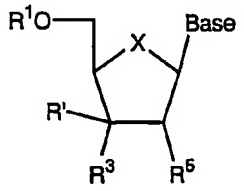
Scheme 4



In another embodiment of the invention, the L-enantiomers are desired. These L-enantiomers corresponding to the compounds of the invention may be prepared following the same general methods given above, but beginning with the corresponding L-sugar or nucleoside L-enantiomer as the starting material.

C. General Synthesis of 3'-C-branched Nucleosides

A 3'-C-branched ribonucleoside of the following structure as an example:



(III)

wherein

R^1, R^3, R^5, and R' are all as defined above;

X is as defined above;

Base is as defined in the specification; or

a pharmaceutically acceptable salt or prodrug thereof; and

all tautomeric, enantiomeric and stereoisomeric forms thereof.

Glycosylation of the nucleoase with an appropriately modified sugar.

The key starting material for this process is an appropriately substituted sugar with a 3'-OH and a 3'-H, with an appropriate leaving group (LG) such as, for example, an acyl group or a halogen. The sugar can be purchased or can be prepared by any known means including standard epimerization, substitution, oxidation and/or reduction techniques. The substituted sugar then can be oxidized by an appropriate oxidizing agent in a compatible solvent at a suitable temperature to yield the 3'-modified sugar.

Possible oxidizing agents include Jones' reagent (a mixture of chromic and sulfuric acids), Collins' reagent (dipyridine Cr(VI)oxide), Corey's reagent (pyridinium chlorochromate), pyridinium dichromate, acid dichromate, potassium permanganate, MnO_2, ruthenium tetroxide, phase transfer catalysts such as chromic acid or permanganate supported on a polymer, Cl_2-pyridine, H_2O_2-ammonium molydate, $NarO_2$-CAN, NaOCl in HOAc, copper chromate, copper oxide, Raney nickel, palladium acetate,

Meerwin-Pondorf-Verley reagent (aluminum *t*-utoxide with another ketone) and *N*-bromosuccinimide.

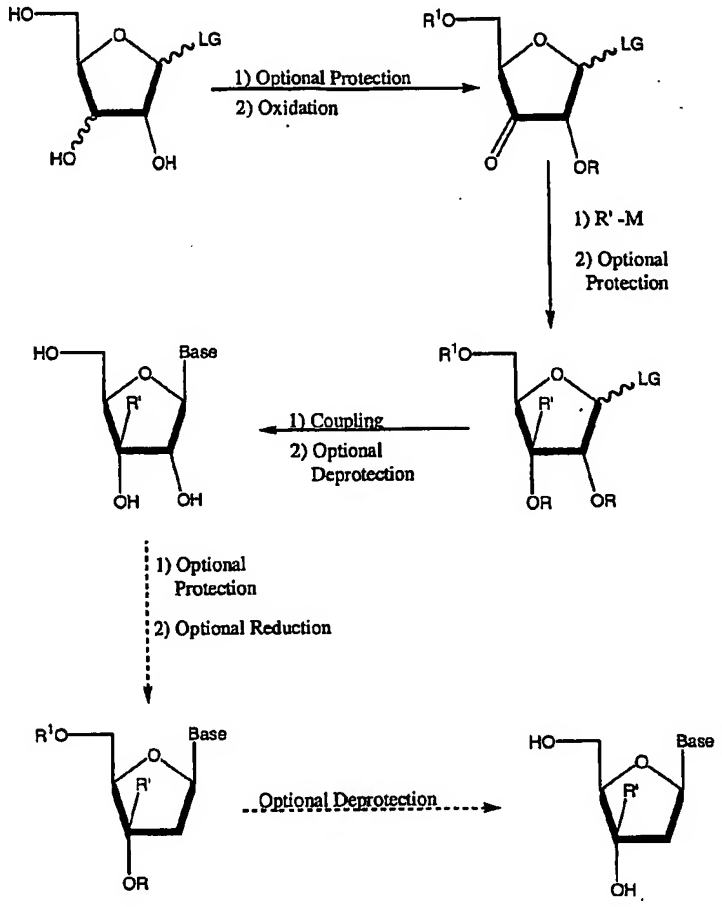
Then coupling of an organometallic carbon nucleophile such as a Grignard reagent, an organolithium, lithium dialkylcopper or R^6-$SiMe_3$ in TAF with the ketone and an appropriate non-protic solvent at a suitable temperature, yields the 3'-C-branched sugar. The 3'-C-branched sugar optionally can e protected with a suitable protecting group, preferably with an acyl or silyl group, by methods well known to those skilled in the art, as taught by Greene et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

The optionally protected sugar can then be coupled to the base by methods well known to those skilled in the art, as taught y Townsend, Chemistry of Nucleosides and Nucleotides, Plenum Press, 1994. For example, an acylated sugar can e coupled to a silylated base with a Lewis acid, such as tin tetrachloride, titanium tetrachloride, or trimethylsilyltriflate in an appropriate solvent at a suitable temperature. Alternatively, a halo-sugar can be coupled to a silylated base in the presence of trimethylsilyltriflate.

Subsequently, the nucleoside can be deprotected by methods well known to those skilled in the art, as by Greene et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

In a particular embodiment, the 3'-C-branched ribonucleoside is desired, the synthesis of which is shown in Scheme 5. Alternatively, a deoxyribonucleoside is desired. To obtain these nucleosides, the formed ribonucleoside can optionally be protected by methods well known to those skilled in the art, as by Greene et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, and then the 2'-OH can be reduced with a suitable reducing agent. Optionally, the 2'-OH can be activated to facilitate reduction, such as, for example, by the Barton reduction.

Scheme 5



Modification of a pre-formed nucleoside.

The key starting material for this process is an appropriately substituted nucleoside with a 3'-OH and 3'-H. The nucleoside can be purchased or can be prepared by any known means including standard coupling techniques. The nucleoside can be optionally protected with suitable protecting groups, preferably with acyl or silyl groups, by methods well known to those skilled in the art, as taught by Greene et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

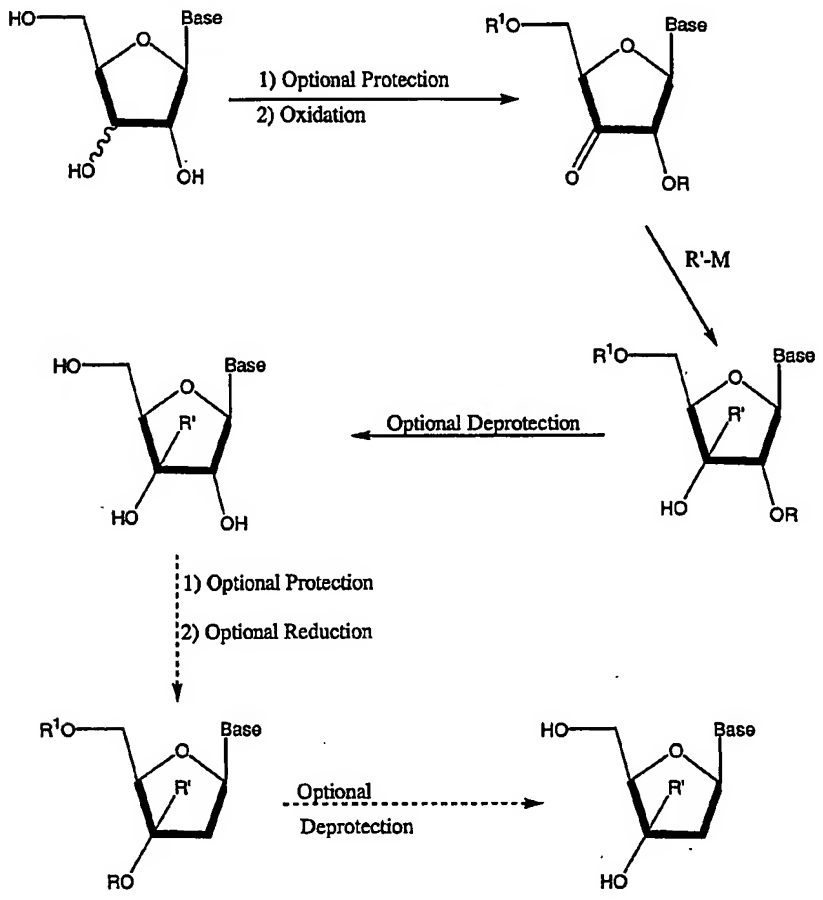
The appropriately protected nucleoside can then be oxidized with the appropriate oxidizing agent in a compatible solvent at a suitable temperature to yield the 2'-modified

sugar. Possible oxidizing agents include Jones' reagent (a mixture of chromic and sulfuric acids), Collins' reagent (dipyridine Cr(VI)oxide), Corey's reagent (pyridinium chlorochromate), pyridinium dichromate, acid dichromate, potassium permanganate, MnO_2, ruthenium tetroxide, phase transfer catalysts such as chromic acid or permanganate supported on a polymer, Cl_2-pyridine, H_2O_2-ammonium molybdate, $NarO_2$-CAN, NaOCl in HOAc, copper chromate, copper oxide, Raney nickel, palladium acetate, Meerwin-Pondorf-Verley reagent (aluminum *t*-butoxide with another ketone) and *N*-bromosuccinimide.

Subsequently, the nucleoside can be deprotected by methods well known to those skilled in the art, as by Greene et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

In a particular embodiment, the 3'-C-branched ribonucleoside is desired, the synthesis of which is shown in Scheme 6. Alternatively, a deoxyribonucleoside is desired. To obtain these nucleosides, the formed ribonucleoside can optionally be protected by methods well known to those skilled in the art, as by Greene et al., Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, and then the 2'-OH can be reduced with a suitable reducing agent. Optionally, the 2'-OH can be activated to facilitate reduction, such as, for example, by the Barton reduction.

Scheme 6



In another embodiment of the invention, the L-enantiomers are desired. These L-enantiomers corresponding to the compounds of the invention may e prepared following the same general methods given above, but beginning with the corresponding L-sugar or nucleoside L-enantiomer as the starting material.

The present invention is described by way of illustration in the following examples. It will be understood by one of ordinary skill in the art that these examples

are in no way limiting and that variations of detail can be made without departing from the spirit and scope of the present invention.

EXAMPLES

Example 1. CC_{50} and EC_{50} Test Results for β-D-2'-C-methyl-adenosine (Compound A) and β-D-2'-C-methyl-2-amino adenosine (Compound B)

	CC_{50}	CC_{50}	CC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}
Compound	MT-4	Vero 76	BHK	Sb-1	CVB-2	CVB-3	CVB-4	CVA-9	REO-1
A	4	80	70	10	10	14	13	12	>70
B	>100	>100	50	90	75	23	32	39	2

Note: Cell lines utilized include MT-4 for HIV; Vero 76, African green monkey kidney cells for SARS-CoV; BHK for Bovine Viral Diarrhea Virus; Sb-1 for poliovirus Sabin type-1; CVB-2, CVB-3, CVB-4, and CVA-9 for Coxsackieviruses B-2, B-3, B-4 and A-9; and REO-1 for double-stranded RNA viruses.

Example 2. CC_{50} and EC_{50} Test Results for β-D-2'-C-methyl-guanosine (Compound C) and β-D-2'-C-methyl-6-chloro-guanosine (Compound D)

	CC_{50}	CC_{50}	CC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}
Cmpd	MT-4	Vero 76	BHK	Sb-1	CVB-2	CVB-3	CVB-4	CVA-9	REO-1
C	>100	>100	100	22	30	22	12	46	2
D	>100	>100	30	50	25	21	25	37	0.4

Example 3. CC_{50} and EC_{50} Test Results for 3',5'-di-*O*-valinyl ester of β-D-2'-C-methyl-guanosine dihydrochloride salt (Compound E)

	CC_{50}	CC_{50}	CC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}
Compound	MT-4	Vero 76	BHK	Sb-1	CVB-2	CVB-3	CVB-4	CVA-9	REO-1
E	>100	>100	100	30	33	30	35	40	2

Example 4. CC_{50} and EC_{50} Test Results for β-D-2'-C-methyl-7-methyl-6-phenyl-3,3a,5,8a-tetrahydro-1,3,4,5,7a-penta-aza-*s*-indacen-8-one (Compound F)

	CC_{50}	CC_{50}	CC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}
Compound	MT-4	Vero 76	BHK	Sb-1	CVB-2	CVB-3	CVB-4	CVA-9	REO-1
F	>100	>100	>100	43	37	49	39	60	2

Example 5. CC_{50} and EC_{50} Test Results for β-D-2'-C-methyl-cytidine (Compound G)

	CC_{50}	CC_{50}	CC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}
Compound	MT-4	Vero 76	BHK	Sb-1	CVB-2	CVB-3	CVB-4	CVA-9	REO-1
G	34	>100	>100	6	11	9	13	26	13

Example 6. CC_{50} and EC_{50} Test Results for β-D-2'-C-ethynyl-adenosine (Compound H)

	CC_{50}	CC_{50}	CC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}
Compound	MT-4	Vero 76	BHK	Sb-1	CVB-2	CVB-3	CVB-4	CVA-9	REO-1
H	4.6	60	15	1	1.5	1	2	2.5	6

Example 7. CC_{50} and EC_{50} Test Results for β-D-2'-C-ethynyl-cytidine (Compound I)

	CC_{50}	CC_{50}	CC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}
Compound	MT-4	Vero 76	BHK	Sb-1	CVB-2	CVB-3	CVB-4	CVA-9	REO-1
I	> or = 100	>100	>100	26	33	33	24	59	>100

5

Example 8. CC_{50} and EC_{50} Test Results for β-D-2-amino-adenosine (Compound J)

	CC_{50}	CC_{50}	CC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}
Compound	MT-4	Vero 76	BHK	Sb-1	CVB-2	CVB-3	CVB-4	CVA-9	REO-1
J	50	>100	>100	40	53	55	50	53	>100

Example 9. CC_{50} Test Results for β-D-2'-C-methyl-adenosine (Compound A), β-D-2'-C-methyl-2-amino adenosine (Compound B), and β-D-2'-C-methyl-2-amino-6-cyclopropyl adenosine(Compound K)

Compound	CC_{50}	BVDV	YFV	WNV	CVB-2	Sb-1	REO
A	4.0	1.2	2.7	3.6	7	7	>70
B	>100	2.1	0.8	0.3	76	90	2
K	>100	18	10	3.5	>100	>100	9.5

Note: BVDV = bovine viral diarrhea virus; YFV = yellow fever virus; WNV = West Nile virus; CVB-2 = Coxsackie B-2 virus; Sb-1 = Sabin type 1 poliomyelitis virus; and REO = double-stranded RNA Reovirus.

Example 10. CC_{50} Test Results for β-D-2'-C-methyl-guanosine (Compound C), β-D-2'-C-methyl-1-(methyl-2-oxo-2-phenyl ethyl)guanosine (Compound L), and β-D-2'-C-methyl-6-chloro guanosine (Compound D)

Compound	CC_{50}	BVDV	YFV	WNV	CVB-2	Sb-1	REO
C	>100	3.5	1.2	0.6	29	50	2
L	>100	12	6	3	>100	>100	12
D	>100	0.7	1.0	0.3	25	50	0.4

Example 11. CC_{50} Test Results for 3',5'-di-*O*-valinyl ester of β-D-2'-C-methyl-guanosine dihydrochloride salt (Compound E)

Compound	CC_{50}	BVDV	YFV	WNV	CVB-2	Sb-1	REO
E	>100	4.9	1.0	1	33	55	2.1

Example 12. CC_{50} Test Results for β-D-2'-C-methyl-7-methyl-6-phenyl-3,3a,5,8a-tetrahydro-1,3,4,5,7a-penta-aza-*s*-indacen-8-one (Compound F)

Compound	CC_{50}	BVDV	YFV	WNV	CVB-2	Sb-1	REO
F	>100	10	2.5	1	37	43	2

Example 13. CC_{50} Test Results for β-D-2'-C-ethynyl-adenosine (Compound H)

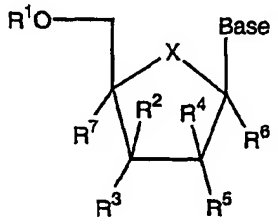
Compound	CC_{50}	BVDV	YFV	WNV	CVB-2	Sb-1	REO
H	4.6	0.4	2.0	1	1.2	0.7	6

Example 14. CC_{50} Test Results for β-D-2'-C-methyl-cytidine (Compound G), 3'-*O*-valinyl ester of β-D-2'-C-methyl-cytidine dihydrochloride salt (Compound M), and β-D-2'-C-methyl-uracil (Compound N)

Compound	CC_{50}	BVDV	YFV	WNV	CVB-2	Sb-1	REO
G	34	2.3	54	80	12	11.5	13
M	24	5.8	82	82	12	14	22
N	>100	18	100	80	>100	55	>100

WE CLAIM:

1. A method of treating a host infected with a coronavirus, togavirus or picornavirus, comprising administering an effective amount of a biologically active nucleoside analogue, wherein the nucleoside analogue has the structure of Formula (AA):



AA

or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein:

R^1 is H; phosphate; mono-, di-, or triphosphate; stabilized phosphate prodrug; optionally substituted acyl; optionally substituted lower acyl; optionally substituted alkyl; optionally substituted lower alkyl; sulfonate ester; alkyl or arylalkyl sulfonyl; methanesulfonyl; aryl; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; optionally substituted arylsulfonyl; a lipid; a phospholipid; an amino acid derivative; a carbohydrate; a peptide; cholesterol; or other pharmaceutically acceptable leaving group that when administered *in vivo*, provides a compound wherein R^1 is independently H or phosphate;

each R^2 and R^4 independently is H, OH, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, halo (F, Cl, Br, I), NO_2, NH_2, N_3, CH_2N_3, CH_2NH_2, CN, CH_2CN, CH_2N_3, CH_2NHCH_3, $CH_2N(CH_3)_2$, CH_2OH, halogenated alkyl, alkoxy, CF_3, $C(A)_3$, 2-Br-ethyl, CH_2F, CH_2Cl, CH_2CF_3, CF_2CF_3, $CH_2(A)$, $C(A)_2(A)_3$, SCN, OCN, NCO, haloalkenyl, Br-vinyl, haloalkynyl; $-(CH_2)_mC(O)OR^{13}$, $-(CH_2)_mC(O)SR^{13}$; -O(alkenyl), $-(CH_2)_mNHR^{13}$, $-(CH_2)_mN(R^{13})_2$, $-(CH_2)_mC(O)NHR^{13}$, $-(CH_2)_mC(O)N(R^{13})_2$, $-C(O)OR^{13}$, $-O(R^{13})$, an optionally substituted carbocycle, an optionally

substituted heterocycle, an optionally substituted heteroaryl, or C_{3-7} cycloalkylamino;

each R^3, R^5 and R^6 independently is H, OH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, halo (F, Cl, Br, or I), NO_2, NH_2, N_3, CH_2N_3, CH_2NH_2, CN, CH_2CN, CH_2N_3, CH_2NHCH_3, $CH_2N(CH_3)_2$, CH_2OH, halogenated alkyl, alkoxy, CF_3, $C(A)_3$, 2-Br-ethyl, CH_2F, CH_2Cl, CH_2CF_3, CF_2CF_3, $CH_2(A)$, $C(A)_2(A)_3$, SCN, OCN, NCO, haloalkenyl, Br-vinyl, haloalkynyl; $-(CH_2)_mC(O)OR^{13}$, $-(CH_2)_mC(O)SR^{13}$; -O(alkenyl), $-(CH_2)_mNHR^{13}$, $-(CH_2)_mN(R^{13})_2$, $-(CH_2)_mC(O)NHR^{13}$, $-(CH_2)_mC(O)N(R^{13})_2$, $-C(O)OR^{13}$, $-O(R^{13})$, an optionally substituted 3-7 membered carbocyclic ring, a C_{3-7} cycloalkylamino, an optionally substituted heterocycle, an optionally substituted heteroaryl, a C_{3-7} cycloalkylamino, CF_3, mercapto, optionally substituted C_{1-4} alkyl, C_{1-12} alkoxy, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{2-6} alkenyloxy, C_{1-4} alkylthio, C_{1-8} alkylcarbonyloxy, aryloxycarbonyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, Br-vinyl, -C(O)O(alkyl), O-phosphate, O-mono-, di-, or triphosphate, O-stabilized phosphate prodrug; O-acyl; O-lower acyl; O-alkyl; O-lower alkyl; O-sulfonate ester, O-alkyl or O-arylalkyl sulfonyl; O-methanesulfonyl; O-benzyl, wherein the phenyl group is optionally substituted with one or more substituents; -OC(O)O-aryl; -OC(O)O-aralkyl; -S(acyl); -S(alkyl); -S(alkenyl); optionally substituted O-arylsulfonyl; an O-linked lipid, including an O-phospholipid; an O-linked amino acid; an O-linked carbohydrate; an O-linked peptide; O-linked cholesterol; or other O-linked pharmaceutically acceptable leaving group that when administered *in vivo*, provides independently OH or O-phosphate;

each R^7 is independently H, $-OR^1$, -OH, $-NO_2$, $-CF_3$, $-NH_2$, Cl, F, Br, I, N_3, CN, optionally substituted alkyl, optionally substituted alkenyl or alkynyl, Br-vinyl, $-CH_2OH$, -O(R), alkoxy, $-(CH_2)_mC(O)O(R)$, -OC(O)O-aryl, -OC(O)O-aralkyl, -SR, $-(CH_2)_mNHR$, $-(CH_2)_mN(R)_2$, or C_{3-7} cycloalkylamino;

each R is H, alkyl, alkenyl, alkynyl, acyl, aryl or aralkyl;

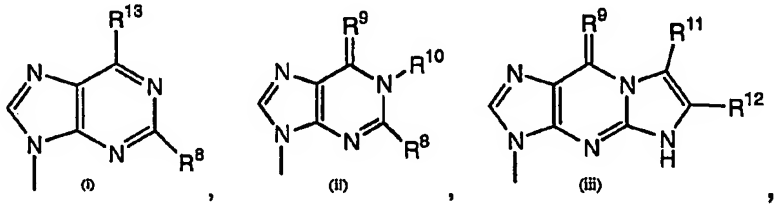
X is O, S, SO_2, CH_2, or CHOH;

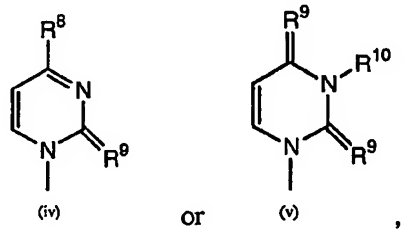
m is 0, 1 or 2;

R^{13} is H, alkyl, alkenyl, alkynyl, acyl, aryl or aralkyl;

A is H, OH, C_{1-4} alkyl, halo (F, Cl, Br, or I), azido, cyano, C_{2-6} alkenyl, C_{2-6} alkynyl, Br-vinyl, 2-Br-ethyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), CF_3, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, or -N(acyl)$_2$; and

Base is a purine, a pyrimidine or a base selected from the group consisting of:





wherein:

each R^8, R^{10}, R^{11}, R^{12} and R^{13} independently is H, NH_2, SH, CF_3, halo, NO_2, N_3, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted phenyl), -NH-cycloalkyl, -NH-cycloalkenyl, -NH-heterocycle, -NH-heteroaryl, -O-cycloalkyl, -O-cycloalkenyl, -O-heterocycle, -O-heteroaryl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{3-6} cycloalkylamino, C_{1-4} alkyl-C(=O)OH, C_{1-4} alkyl-C(=O)O-aryl, C_{1-4} alkyl-C(=O)O-phenyl, C_{1-4} alkyl-C(=O)O-heterocycle, C_{1-4} alkyl-C(=O)O-heteroaryl, or C_{1-4} alkoxy; and

R^9 is O or S;

optionally in a pharmaceutically acceptable carrier or diluent.

2. The method of claim 1, wherein the coronavirus is a SARS-CoV virus.

3. The method of claim 1, wherein the togavirus is a rubivirus (the causative agent for rubella) or an alphavirus (the causative agent for encephalitis)

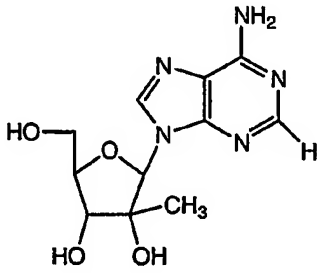
4. The method of claim 1, wherein the a picornavirus is an enterovirus, a rhinovirus, a cardiovirus or an aphthovirus.

5. The method of claim 4, wherein the enterovirus is a Coxsackievirus, poliovirus, hepatitis A virus, echovirus, or a human enterovirus species.

6. The method of claim 1 wherein the host is a mammal.

7. The method of claim 6 wherein the mammal is a human.

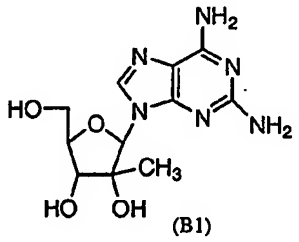
8. The method of claim 1 wherein the compound of Formula (AA) has the structure of (A1):



(A1)

or a pharmaceutically acceptable salt or prodrug thereof.

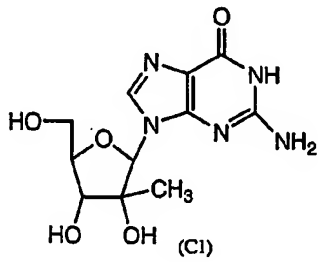
9. The method of claim 1 wherein the compound of Formula (AA) has the structure of (B1):



(B1)

or a pharmaceutically acceptable salt or prodrug thereof.

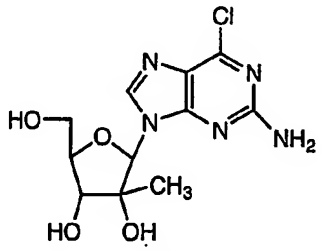
10. The method of claim 1 wherein the compound of Formula (AA) has the structure of (C1):



(C1)

or a pharmaceutically acceptable salt or prodrug thereof.

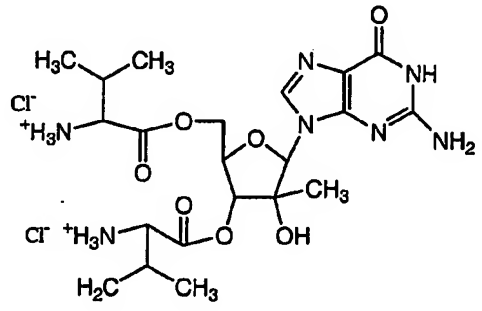
11. The method of claim 1 wherein the compound of Formula (AA) has the structure of (D1):



(D1)

or a pharmaceutically acceptable salt or prodrug thereof.

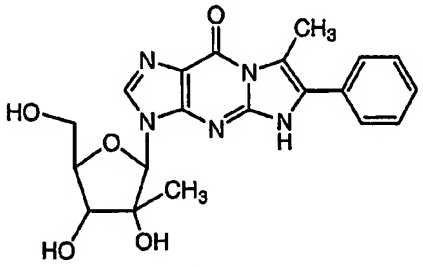
12. The method of claim 1 wherein the compound of Formula (AA) has the structure of (E1):



(E1)

or a pharmaceutically acceptable salt or prodrug thereof.

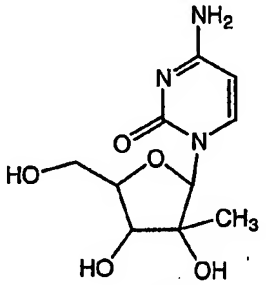
13. The method of claim 1 wherein the compound of Formula (AA) has the structure of (F1):



(F1)

or a pharmaceutically acceptable salt or prodrug thereof.

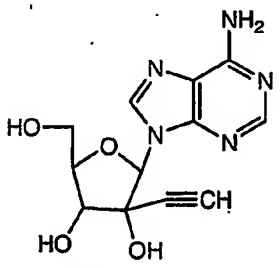
14. The method of claim 1 wherein the compound of Formula (AA) has the structure of (G1):



(G1)

or a pharmaceutically acceptable salt or prodrug thereof.

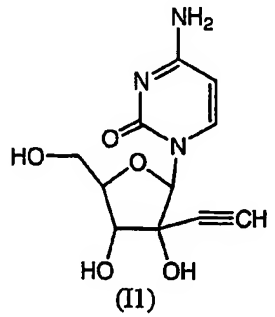
15. The method of claim 1 wherein the compound of Formula (AA) has the structure of (H1):



(H1)

or a pharmaceutically acceptable salt or prodrug thereof.

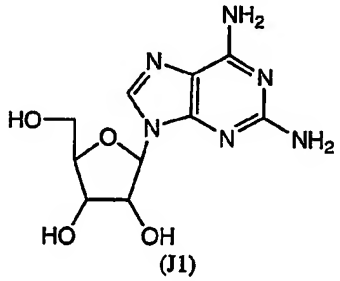
16. The method of claim 1 wherein the compound of Formula (AA) has the structure of (I1):



(I1)

or a pharmaceutically acceptable salt or prodrug thereof.

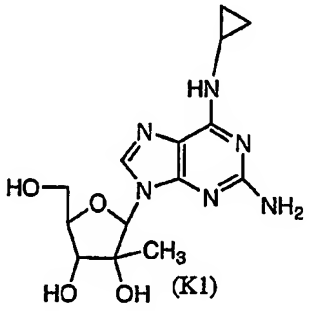
17. The method of claim 1 wherein the compound of Formula (AA) has the structure of (J1):



(J1)

or a pharmaceutically acceptable salt or prodrug thereof.

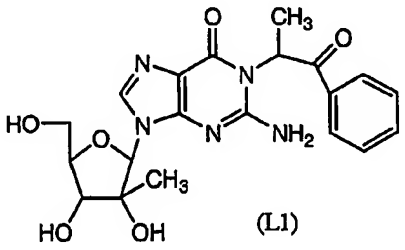
18. The method of claim 1 wherein the compound of Formula (AA) has the structure of (K1):



(K1)

or a pharmaceutically acceptable salt or prodrug thereof.

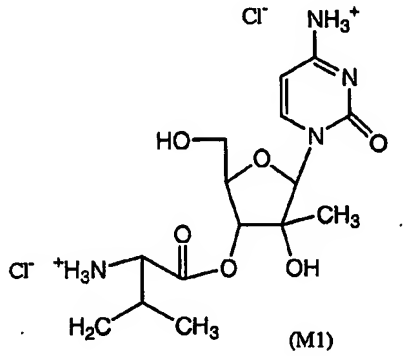
19. The method of claim 1 wherein the compound of Formula (AA) has the structure of (L1):



(L1)

or a pharmaceutically acceptable salt or prodrug thereof.

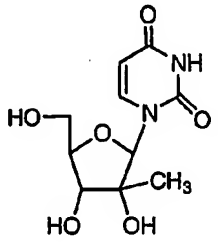
20. The method of claim 1 wherein the compound of Formula (AA) has the structure of (M1):



(M1)

or a pharmaceutically acceptable salt or prodrug thereof.

21. The method of claim 1 wherein the compound of Formula (AA) has the structure of (N1):



(N1)

or a pharmaceutically acceptable salt or prodrug thereof.

22. The method of claim 1 wherein the compound of Formula (AA) is administered in combination and/or alternation with one or more other anti-viral agent.

23. The method of claim 22, wherein the other anti-viral agent is an anti-coronavirus, anti-togavirus, and/or anti-picornavirus agent.

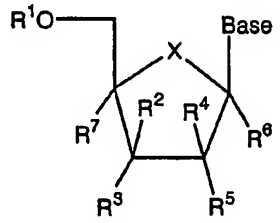
24. The method of claim 23, wherein the anti-coronavirus agent is an anti-SARS-CoV agent.

25. The method of claim 23, wherein the anti-togavirus agent is an anti-rubivirus or an anti-alphavirus agent.

26. The method of claim 23, wherein the anti-picornavirus is an anti-enterovirus, anti-rhinovirus, anti-cardiovirus and/or anti-aphthovirus agent.

27. The method of claim 26, wherein the anti-enterovirus agent is an anti-Coxsackievirus, anti-poliovirus, anti-hepatitis A virus, and/or an anti-echovirus agent.

28. A pharmaceutical composition for the treatment of a coronavirus, togavirus or picornavirus comprising a treatment effective amount of a nucleoside analogue of the structure of Formula (AA):



AA

or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein:

R^1 is H; phosphate; mono-, di-, or triphosphate; stabilized phosphate prodrug; optionally substituted acyl; optionally substituted lower acyl; optionally substituted alkyl; optionally substituted lower alkyl; sulfonate ester; alkyl or arylalkyl sulfonyl; methanesulfonyl; aryl; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; optionally substituted arylsulfonyl; a lipid; a phospholipid; an amino acid derivative; a

carbohydrate; a peptide; cholesterol; or other pharmaceutically acceptable leaving group that when administered *in vivo*, provides a compound wherein R^1 is independently H or phosphate;

each R^2 and R^4 independently is H, OH, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, halo (F, Cl, Br, I), NO_2, NH_2, N_3, CH_2N_3, CH_2NH_2, CN, CH_2CN, CH_2N_3, CH_2NHCH_3, $CH_2N(CH_3)_2$, CH_2OH, halogenated alkyl, alkoxy, CF_3, $C(A)_3$, 2-Br-ethyl, CH_2F, CH_2Cl, CH_2CF_3, CF_2CF_3, $CH_2(A)$, $C(A)_2(A)_3$, SCN, OCN, NCO, haloalkenyl, Br-vinyl, haloalkynyl; $-(CH_2)_mC(O)OR^{13}$, $-(CH_2)_mC(O)SR^{13}$; -O(alkenyl), $-(CH_2)_mNHR^{13}$, $-(CH_2)_mN(R^{13})_2$, $-(CH_2)_mC(O)NHR^{13}$, $-(CH_2)_mC(O)N(R^{13})_2$, $-C(O)OR^{13}$, $-O(R^{13})$, an optionally substituted carbocycle, an optionally substituted heterocycle, an optionally substituted heteroaryl, or C_{3-7} cycloalkylamino;

each R^3, R^5 and R^6 independently is H, OH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, halo (F, Cl, Br, or I), NO_2, NH_2, N_3, CH_2N_3, CH_2NH_2, CN, CH_2CN, CH_2N_3, CH_2NHCH_3, $CH_2N(CH_3)_2$, CH_2OH, halogenated alkyl, alkoxy, CF_3, $C(A)_3$, 2-Br-ethyl, CH_2F, CH_2Cl, CH_2CF_3, CF_2CF_3, $CH_2(A)$, $C(A)_2(A)_3$, SCN, OCN, NCO, haloalkenyl, Br-vinyl, haloalkynyl; $-(CH_2)_mC(O)OR^{13}$, $-(CH_2)_mC(O)SR^{13}$; -O(alkenyl), $-(CH_2)_mNHR^{13}$, $-(CH_2)_mN(R^{13})_2$, $-(CH_2)_mC(O)NHR^{13}$, $-(CH_2)_mC(O)N(R^{13})_2$, $-C(O)OR^{13}$, $-O(R^{13})$, an optionally substituted 3-7 membered carbocyclic ring, a C_{3-7} cycloalkylamino, an optionally substituted heterocycle, an optionally substituted heteroaryl, a C_{3-7} cycloalkylamino, CF_3, mercapto, optionally substituted C_{1-4} alkyl, C_{1-12} alkoxy, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{2-6} alkenyloxy, C_{1-4} alkylthio, C_{1-8} alkylcarbonyloxy, aryloxycarbonyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, Br-vinyl, -C(O)O(alkyl), O-phosphate, O-mono-, di-, or triphosphate, O-stabilized phosphate prodrug; O-acyl; O-lower acyl; O-alkyl; O-lower alkyl; O-sulfonate ester, O-alkyl or O-arylalkyl sulfonyl; O-methanesulfonyl; O-benzyl, wherein the phenyl group is optionally substituted with one or more substituents; -OC(O)O-aryl; -OC(O)O-aralkyl; -S(acyl); -S(alkyl); -S(alkenyl); optionally substituted O-arylsulfonyl; an O-linked lipid, including

an O-phospholipid; an O-linked amino acid; an O-linked carbohydrate; an O-linked peptide; O-linked cholesterol; or other O-linked pharmaceutically acceptable leaving group that when administered *in vivo*, provides independently OH or O-phosphate;

each R^7 is independently H, $-OR^1$, -OH, $-NO_2$, $-CF_3$, $-NH_2$, Cl, F, Br, I, N_3, CN, optionally substituted alkyl, optionally substituted alkenyl or alkynyl, Br-vinyl, $-CH_2OH$, -O(R), alkoxy, $-(CH_2)_mC(O)O(R)$, -OC(O)O-aryl, -OC(O)O-aralkyl, -SR, $-(CH_2)_mNHR$, $-(CH_2)_mN(R)_2$, or C_{3-7} cycloalkylamino;

each R is H, alkyl, alkenyl, alkynyl, acyl, aryl or aralkyl;

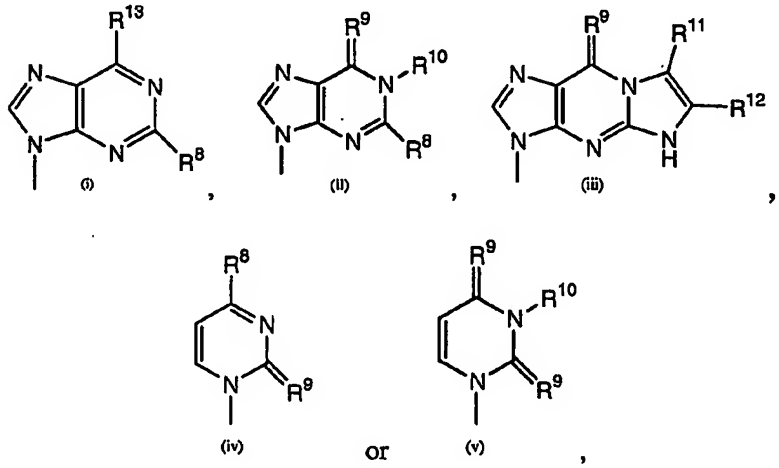
X is O, S, SO_2, CH_2, or CHOH;

m is 0, 1 or 2;

R^{13} is H, alkyl, alkenyl, alkynyl, acyl, aryl or aralkyl;

A is H, OH, C_{1-4} alkyl, halo (F, Cl, Br, or I), azido, cyano, C_{2-6} alkenyl, C_{2-6} alkynyl, Br-vinyl, 2-Br-ethyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), CF_3, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, or -N(acyl)$_2$; and

Base is a purine, pyrimidine, or a base selected from the group consisting of:



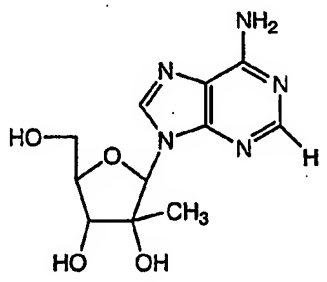
wherein:

each R^8, R^{10}, R^{11}, R^{12} and R^{13} independently is H, NH_2, SH, CF_3, halo, NO_2, N_3, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted phenyl, -NH-cycloalkyl, -NH-cycloalkenyl, -NH-heterocycle, -NH-heteroaryl, -O-cycloalkyl, -O-cycloalkenyl, -O-heterocycle, -O-heteroaryl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{3-6} cycloalkylamino, C_{1-4} alkyl-C(=O)OH, C_{1-4} alkyl-C(=O)O-aryl, C_{1-4} alkyl-C(=O)O-phenyl, C_{1-4} alkyl-C(=O)O-heterocycle, C_{1-4} alkyl-C(=O)O-heteroaryl, or C_{1-4} alkoxy; and

R^9 is O or S;

optionally in combination with one or more other effective anti-coronavirus, anti-picornavirus, and/or anti-togavirus agents, optionally in a pharmaceutically acceptable carrier or diluent.

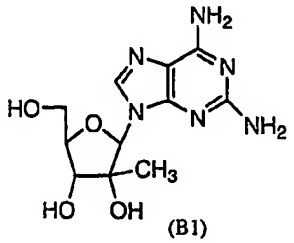
29. The pharmaceutical composition of claim 28 wherein the compound of Formula (AA) has the structure of (A1):



(A1)

or a pharmaceutically acceptable salt or prodrug thereof.

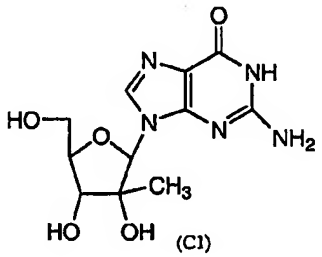
30. The pharmaceutical composition of claim 28 wherein the compound of Formula (AA) has the structure of (B1):



(B1)

or a pharmaceutically acceptable salt or prodrug thereof.

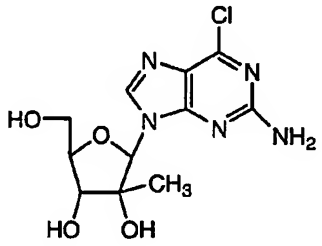
31. The pharmaceutical composition of claim 28 wherein the compound of Formula (AA) has the structure of (C1):



(C1)

or a pharmaceutically acceptable salt or prodrug thereof.

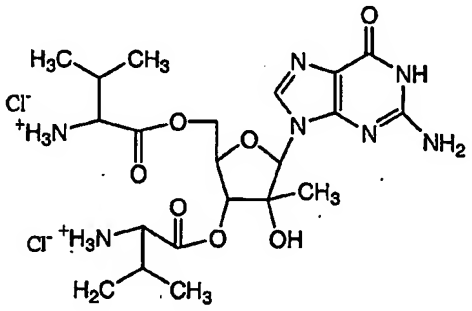
32. The pharmaceutical composition of claim 28 wherein the compound of Formula (AA) has the structure of (D1):



(D1)

or a pharmaceutically acceptable salt or prodrug thereof.

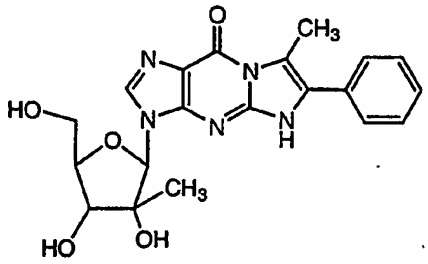
33. The pharmaceutical composition of claim 28 wherein the compound of Formula (AA) has the structure of (E1):



(E1)

or a pharmaceutically acceptable salt or prodrug thereof.

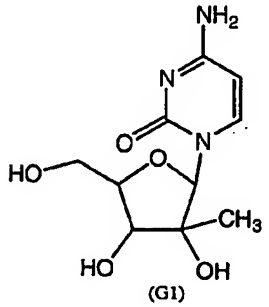
34. The pharmaceutical composition of claim 28 wherein the compound of Formula (AA) has the structure of (F1):



(F1)

or a pharmaceutically acceptable salt or prodrug thereof.

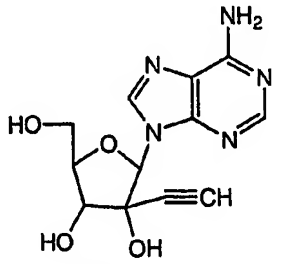
35. The pharmaceutical composition of claim 28 wherein the compound of Formula (AA) has the structure of (G1):



(G1)

or a pharmaceutically acceptable salt or prodrug thereof.

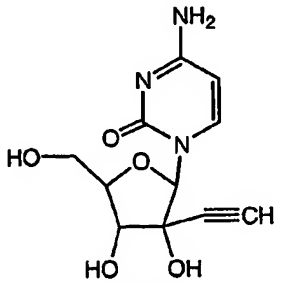
36. The pharmaceutical composition of claim 28 wherein the compound of Formula (AA) has the structure of (H1):



(H1)

or a pharmaceutically acceptable salt or prodrug thereof.

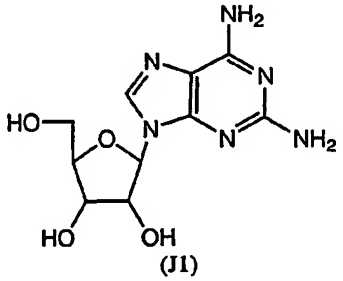
37. The pharmaceutical composition of claim 28 wherein the compound of Formula (AA) has the structure of (I1):



(I1)

or a pharmaceutically acceptable salt or prodrug thereof.

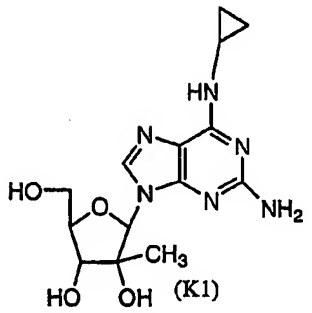
38. The pharmaceutical composition of claim 28 wherein the compound of Formula (AA) has the structure of (J1):



(J1)

or a pharmaceutically acceptable salt or prodrug thereof.

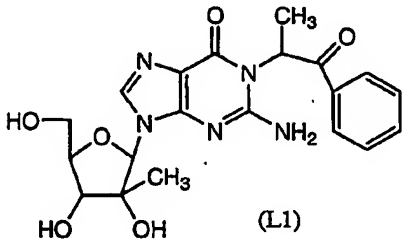
39. The pharmaceutical composition of claim 28 wherein the compound of Formula (AA) has the structure of (K1):



(K1)

or a pharmaceutically acceptable salt or prodrug thereof.

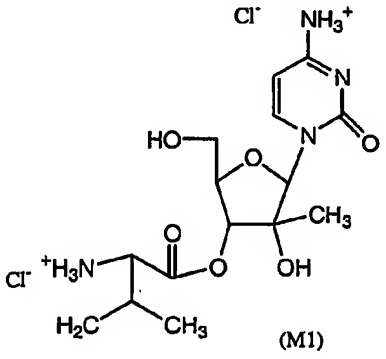
40. The pharmaceutical composition of claim 28 wherein the compound of Formula (AA) has the structure of (L1):



(L1)

or a pharmaceutically acceptable salt or prodrug thereof.

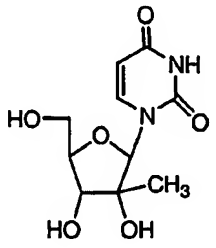
41. The pharmaceutical composition of claim 28 wherein the compound of Formula (AA) has the structure of (M1):



(M1)

or a pharmaceutically acceptable salt or prodrug thereof.

42. The pharmaceutical composition of claim 28 wherein the compound of Formula (AA) has the structure of (N1):



(N1)

or a pharmaceutically acceptable salt or prodrug thereof.

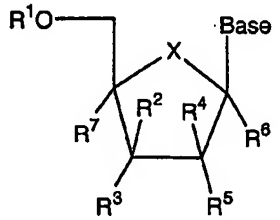
43. The pharmaceutical composition of claim 28, wherein the anti-coronavirus agent is an anti-SARS-CoV agent.

44. The pharmaceutical composition of claim 28, wherein the anti-togavirus agent is an anti-rubivirus or an anti-alphavirus agent.

45. The pharmaceutical composition of claim 28, wherein the anti-picornavirus is an anti-enterovirus, anti-rhinovirus, anti-cardiovirus and/or anti-aphthovirus agent.

46. The pharmaceutical composition of claim 45, wherein the anti-enterovirus agent is an anti-Coxsackievirus, anti-poliovirus, anti-hepatitis A virus, and/or an anti-echovirus agent.

47. Use of an effective amount of compound of the structure of Formula (AA):



AA

or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein:

R^1 is H; phosphate; mono-, di-, or triphosphate; stabilized phosphate prodrug; optionally substituted acyl; optionally substituted lower acyl; optionally substituted alkyl; optionally substituted lower alkyl; sulfonate ester; alkyl or

arylalkyl sulfonyl; methanesulfonyl; aryl; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; optionally substituted arylsulfonyl; a lipid; a phospholipid; an amino acid derivative; a carbohydrate; a peptide; cholesterol; or other pharmaceutically acceptable leaving group that when administered *in vivo*, provides a compound wherein R^1 is independently H or phosphate;

each R^2 and R^4 independently is H, OH, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, halo (F, Cl, Br, I), NO_2, NH_2, N_3, CH_2N_3, CH_2NH_2, CN, CH_2CN, CH_2N_3, CH_2NHCH_3, $CH_2N(CH_3)_2$, CH_2OH, halogenated alkyl, alkoxy, CF_3, $C(A)_3$, 2-Br-ethyl, CH_2F, CH_2Cl, CH_2CF_3, CF_2CF_3, $CH_2(A)$, $C(A)_2(A)_3$, SCN, OCN, NCO, haloalkenyl, Br-vinyl, haloalkynyl; $-(CH_2)_mC(O)OR^{13}$, $-(CH_2)_mC(O)SR^{13}$; -O(alkenyl), $-(CH_2)_mNHR^{13}$, $-(CH_2)_mN(R^{13})_2$, $-(CH_2)_mC(O)NHR^{13}$, $-(CH_2)_mC(O)N(R^{13})_2$, $-C(O)OR^{13}$, $-O(R^{13})$, an optionally substituted carbocycle, an optionally substituted heterocycle, an optionally substituted heteroaryl, or C_{3-7} cycloalkylamino;

each R^3, R^5 and R^6 independently is H, OH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, halo (F, Cl, Br, or I), NO_2, NH_2, N_3, CH_2N_3, CH_2NH_2, CN, CH_2CN, CH_2N_3, CH_2NHCH_3, $CH_2N(CH_3)_2$, CH_2OH, halogenated alkyl, alkoxy, CF_3, $C(A)_3$, 2-Br-ethyl, CH_2F, CH_2Cl, CH_2CF_3, CF_2CF_3, $CH_2(A)$, $C(A)_2(A)_3$, SCN, OCN, NCO, haloalkenyl, Br-vinyl, haloalkynyl; $-(CH_2)_mC(O)OR^{13}$, $-(CH_2)_mC(O)SR^{13}$; -O(alkenyl), $-(CH_2)_mNHR^{13}$, $-(CH_2)_mN(R^{13})_2$, $-(CH_2)_mC(O)NHR^{13}$, $-(CH_2)_mC(O)N(R^{13})_2$, $-C(O)OR^{13}$, $-O(R^{13})$, an optionally substituted 3-7 membered carbocyclic ring, a C_{3-7} cycloalkylamino, an optionally substituted heterocycle, an optionally substituted heteroaryl, a C_{3-7} cycloalkylamino, CF_3, mercapto, optionally substituted C_{1-4} alkyl, C_{1-12} alkoxy, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{2-6} alkenyloxy, C_{1-4} alkylthio, C_{1-8} alkylcarbonyloxy, aryloxycarbonyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, Br-vinyl, -C(O)O(alkyl), O-phosphate, O-mono-, di-, or triphosphate, O-stabilized phosphate prodrug; O-acyl; O-lower acyl; O-alkyl; O-lower alkyl; O-sulfonate ester, O-alkyl or O-arylalkyl sulfonyl; O-methanesulfonyl; O-

benzyl, wherein the phenyl group is optionally substituted with one or more substituents; -OC(O)O-aryl; -OC(O)O-aralkyl; -S(acyl); -S(alkyl); -S(alkenyl); optionally substituted O-arylsulfonyl; an O-linked lipid, including an O-phospholipid; an O-linked amino acid; an O-linked carbohydrate; an O-linked peptide; O-linked cholesterol; or other O-linked pharmaceutically acceptable leaving group that when administered *in vivo*, provides independently OH or O-phosphate;

each R^7 is independently H, $-OR^1$, -OH, $-NO_2$, $-CF_3$, $-NH_2$, Cl, F, Br, I, N_3, CN, optionally substituted alkyl, optionally substituted alkenyl or alkynyl, Br-vinyl, $-CH_2OH$, -O(R), alkoxy, $-(CH_2)_mC(O)O(R)$, -OC(O)O-aryl, -OC(O)O-aralkyl, -SR, $-(CH_2)_mNHR$, $-(CH_2)_mN(R)_2$, or C_{3-7} cycloalkylamino;

each R is H, alkyl, alkenyl, alkynyl, acyl, aryl or aralkyl;

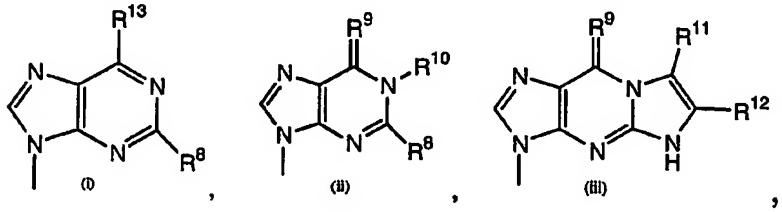
X is O, S, SO_2, CH_2, or CHOH;

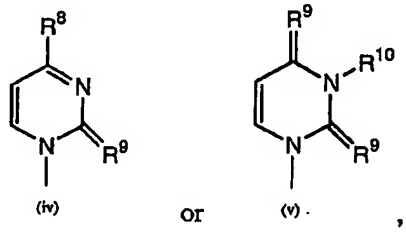
m is 0, 1 or 2;

R^{13} is H, alkyl, alkenyl, alkynyl, acyl, aryl or aralkyl;

A is H, OH, C_{1-4} alkyl, halo (F, Cl, Br, or I), azido, cyano, C_{2-6} alkenyl, C_{2-6} alkynyl, Br-vinyl, 2-Br-ethyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), CF_3, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, or -N(acyl)$_2$; and

Base is a purine, a pyrimidine or a base selected from the group consisting of:





wherein:

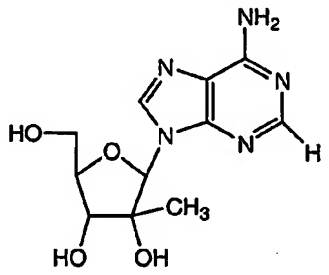
each R^8, R^{10}, R^{11}, R^{12} and R^{13} independently is H, NH_2, SH, CF_3, halo, NO_2, N_3, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted phenyl, -NH-cycloalkyl, -NH-cycloalkenyl, -NH-heterocycle, -NH-heteroaryl, -O-cycloalkyl, -O-cycloalkenyl, -O-heterocycle, -O-heteroaryl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{3-6} cycloalkylamino, C_{1-4} alkyl-C(=O)OH, C_{1-4} alkyl-C(=O)O-aryl, C_{1-4} alkyl-C(=O)O-phenyl), C_{1-4} alkyl-C(=O)O-heterocycle, C_{1-4} alkyl-C(=O)O-heteroaryl, or C_{1-4} alkoxy; and

R^9 is O or S;

optionally in a pharmaceutically acceptable carrier or diluent;

for the treatment of a coronavirus, togavirus or picornavirus infection in a host.

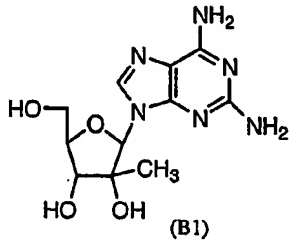
48. The use of claim 47 wherein the compound of Formula (AA) has the structure of (A1):



(A1)

or a pharmaceutically acceptable salt or prodrug thereof.

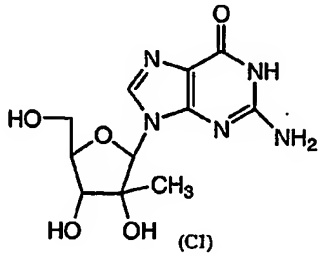
49. The use of claim 47 wherein the compound of Formula (AA) has the structure of (B1):



(B1)

or a pharmaceutically acceptable salt or prodrug thereof.

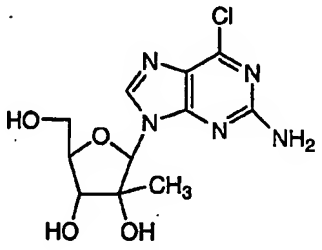
50. The use of claim 47 wherein the compound of Formula (AA) has the structure of (C1):



(CI)

or a pharmaceutically acceptable salt or prodrug thereof.

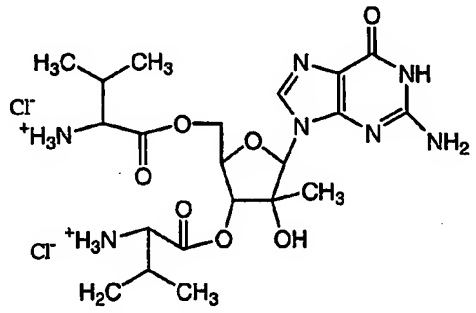
51. The use of claim 47 wherein the compound of Formula (AA) has the structure of (D1):



(D1)

or a pharmaceutically acceptable salt or prodrug thereof.

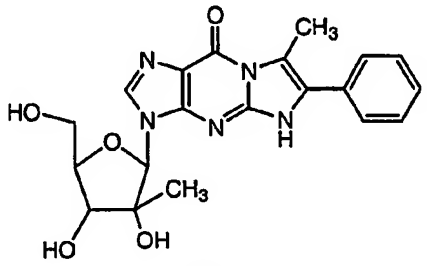
52. The use of claim 47 wherein the compound of Formula (AA) has the structure of (E1):



(E1)

or a pharmaceutically acceptable salt or prodrug thereof.

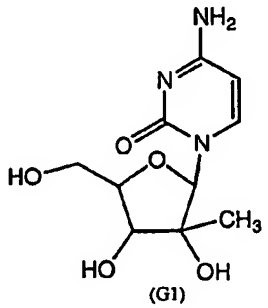
53. The use of claim 47 wherein the compound of Formula (AA) has the structure of (F1):



(F1)

or a pharmaceutically acceptable salt or prodrug thereof.

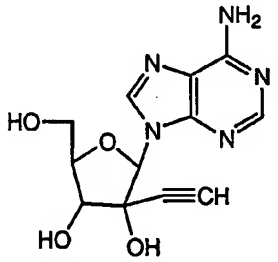
54. The use of claim 47 wherein the compound of Formula (AA) has the structure of (G1):



(G1)

or a pharmaceutically acceptable salt or prodrug thereof.

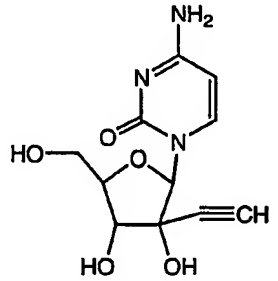
55. The use of claim 47 wherein the compound of Formula (AA) has the structure of (H1):



(H1)

or a pharmaceutically acceptable salt or prodrug thereof.

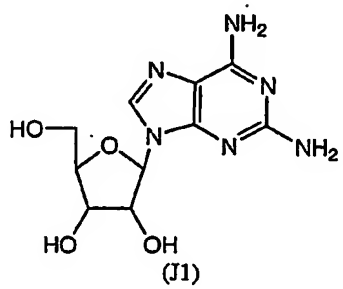
56. The use of claim 47 wherein the compound of Formula (AA) has the structure of (I1):



(I1)

or a pharmaceutically acceptable salt or prodrug thereof.

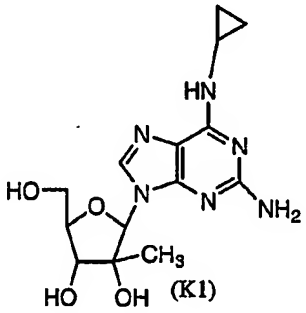
57. The use of claim 47 wherein the compound of Formula (AA) has the structure of (J1):



(J1)

or a pharmaceutically acceptable salt or prodrug thereof.

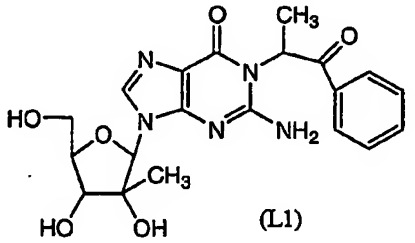
58. The use of claim 47 wherein the compound of Formula (AA) has the structure of (K1):



(K1)

or a pharmaceutically acceptable salt or prodrug thereof.

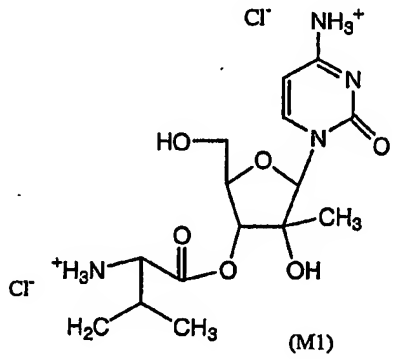
59. The use of claim 47 wherein the compound of Formula (AA) has the structure of (L1):



(L1)

or a pharmaceutically acceptable salt or prodrug thereof.

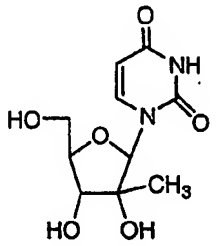
60. The use of claim 47 wherein the compound of Formula (AA) has the structure of (M1):



(M1)

or a pharmaceutically acceptable salt or prodrug thereof.

61. The use of claim 47 wherein the compound of Formula (AA) has the structure of (N1):



(N1)

or a pharmaceutically acceptable salt or prodrug thereof.

62. The use of claim any one of claims 47-61, further in combination and/or alternation with one or more other anti-viral agent.

63. The use of claim 62, wherein the other anti-viral agent is an anti-coronavirus, anti-togavirus, and/or anti-picornavirus agent.

64. The use of claim 63, wherein the anti-coronavirus agent is an anti-SARS-CoV agent.

65. The use of claim 63, wherein the anti-togavirus agent is an anti-rubivirus or an anti-alphavirus agent.

66. The use of claim 63, wherein the anti-picornavirus is an anti-enterovirus, anti-rhinovirus, anti-cardiovirus and/or anti-aphthovirus agent.

67. The use of claim 66, wherein the anti-enterovirus agent is an anti-Coxsackievirus, anti-poliovirus, anti-hepatitis A virus, and/or an anti-echovirus agent.

68. The use of any one of claims 47-67, wherein the coronavirus is a SARS-CoV virus.

69. The use of any one of claims 47-67, wherein the togavirus is a rubivirus (the causative agent for rubella) or an alphavirus (the causative agent for encephalitis)

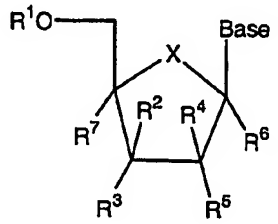
70. The use of any one of claims 47-67, wherein the a picornavirus is an enterovirus, a rhinovirus, a cardiovirus or an aphthovirus.

71. The use of claim 70, wherein the enterovirus is a Coxsackievirus, poliovirus, hepatitis A virus, echovirus, or a human enterovirus species.

72. The use of any one of claims 47-71 wherein the host is a mammal.

73. The use of claim 72 wherein the mammal is a human.

74. Use of an effective amount of a compound of the structure of Formula (AA):



AA

or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein:

R^1 is H; phosphate; mono-, di-, or triphosphate; stabilized phosphate prodrug; optionally substituted acyl; optionally substituted lower acyl; optionally substituted alkyl; optionally substituted lower alkyl; sulfonate ester; alkyl or arylalkyl sulfonyl; methanesulfonyl; aryl; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; optionally substituted arylsulfonyl; a lipid; a phospholipid; an amino acid derivative; a carbohydrate; a peptide; cholesterol; or other pharmaceutically acceptable leaving group that when administered *in vivo*, provides a compound wherein R^1 is independently H or phosphate;

each R^2 and R^4 independently is H, OH, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, halo (F, Cl, Br, I), NO_2, NH_2, N_3, CH_2N_3, CH_2NH_2, CN, CH_2CN, CH_2N_3, CH_2NHCH_3, $CH_2N(CH_3)_2$, CH_2OH, halogenated alkyl, alkoxy, CF_3, $C(A)_3$, 2-Br-ethyl, CH_2F, CH_2Cl, CH_2CF_3, CF_2CF_3, $CH_2(A)$, $C(A)_2(A)_3$, SCN, OCN, NCO, haloalkenyl, Br-vinyl, haloalkynyl; $-(CH_2)_mC(O)OR^{13}$, $-(CH_2)_mC(O)SR^{13}$; -O(alkenyl), $-(CH_2)_mNHR^{13}$, $-(CH_2)_mN(R^{13})_2$, $-(CH_2)_mC(O)NHR^{13}$, $-(CH_2)_mC(O)N(R^{13})_2$, $-C(O)OR^{13}$, $-O(R^{13})$, an optionally substituted carbocycle, an optionally

substituted heterocycle, an optionally substituted heteroaryl, or C_{3-7} cycloalkylamino;

each R^3, R^5 and R^6 independently is H, OH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, halo (F, Cl, Br, or I), NO_2, NH_2, N_3, CH_2N_3, CH_2NH_2, CN, CH_2CN, CH_2N_3, CH_2NHCH_3, $CH_2N(CH_3)_2$, CH_2OH, halogenated alkyl, alkoxy, CF_3, $C(A)_3$, 2-Br-ethyl, CH_2F, CH_2Cl, CH_2CF_3, CF_2CF_3, $CH_2(A)$, $C(A)_2(A)_3$, SCN, OCN, NCO, haloalkenyl, Br-vinyl, haloalkynyl; $-(CH_2)_mC(O)OR^{13}$, $-(CH_2)_mC(O)SR^{13}$; -O(alkenyl), $-(CH_2)_mNHR^{13}$, $-(CH_2)_mN(R^{13})_2$, $-(CH_2)_mC(O)NHR^{13}$, $-(CH_2)_mC(O)N(R^{13})_2$, $-C(O)OR^{13}$, $-O(R^{13})$, an optionally substituted 3-7 membered carbocyclic ring, a C_{3-7} cycloalkylamino, an optionally substituted heterocycle, an optionally substituted heteroaryl, a C_{3-7} cycloalkylamino, CF_3, mercapto, optionally substituted C_{1-4} alkyl, C_{1-12} alkoxy, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{2-6} alkenyloxy, C_{1-4} alkylthio, C_{1-8} alkylcarbonyloxy, aryloxycarbonyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, Br-vinyl, -C(O)O(alkyl), O-phosphate, O-mono-, di-, or triphosphate, O-stabilized phosphate prodrug; O-acyl; O-lower acyl; O-alkyl; O-lower alkyl; O-sulfonate ester, O-alkyl or O-arylalkyl sulfonyl; O-methanesulfonyl; O-benzyl, wherein the phenyl group is optionally substituted with one or more substituents; -OC(O)O-aryl; -OC(O)O-aralkyl; -S(acyl); -S(alkyl); -S(alkenyl); optionally substituted O-arylsulfonyl; an O-linked lipid, including an O-phospholipid; an O-linked amino acid; an O-linked carbohydrate; an O-linked peptide; O-linked cholesterol; or other O-linked pharmaceutically acceptable leaving group that when administered *in vivo*, provides independently OH or O-phosphate;

each R^7 is independently H, $-OR^1$, -OH, $-NO_2$, $-CF_3$, $-NH_2$, Cl, F, Br, I, N_3, CN, optionally substituted alkyl, optionally substituted alkenyl or alkynyl, Br-vinyl, $-CH_2OH$, -O(R), alkoxy, $-(CH_2)_mC(O)O(R)$, -OC(O)O-aryl, -OC(O)O-aralkyl, -SR, $-(CH_2)_mNHR$, $-(CH_2)_mN(R)_2$, or C_{3-7} cycloalkylamino;

each R is H, alkyl, alkenyl, alkynyl, acyl, aryl or aralkyl;

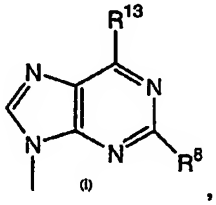
X is O, S, SO_2, CH_2, or CHOH;

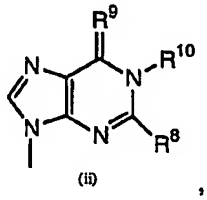
m is 0, 1 or 2;

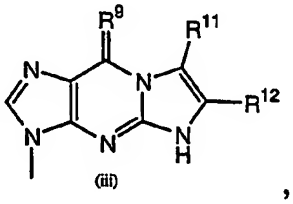
R^{13} is H, alkyl, alkenyl, alkynyl, acyl, aryl or aralkyl;

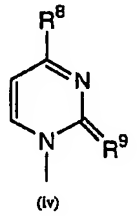
A is H, OH, C_{1-4} alkyl, halo (F, Cl, Br, or I), azido, cyano, C_{2-6} alkenyl, C_{2-6} alkynyl, Br-vinyl, 2-Br-ethyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), CF_3, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, or -N(acyl)$_2$; and

Base is a purine, pyrimidine or a base selected from the group consisting of:

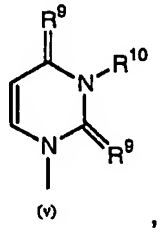

(i)


(ii)


(iii)


(iv)

or


(v)

wherein:

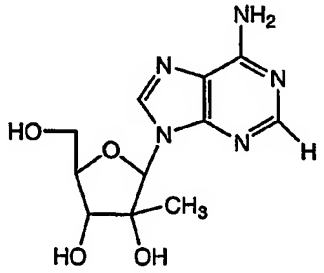
each R^8, R^{10}, R^{11}, R^{12} and R^{13} independently is H, NH_2, SH, CF_3, halo, NO_2, N_3, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted phenyl), -NH-cycloalkyl, -NH-cycloalkenyl, -NH-heterocycle, -NH-heteroaryl, -O-cycloalkyl, -O-cycloalkenyl, -O-heterocycle, -O-heteroaryl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{3-6} cycloalkylamino, C_{1-4} alkyl-C(=O)OH, C_{1-4} alkyl-C(=O)O-aryl, C_{1-4} alkyl-C(=O)O-phenyl, C_{1-4} alkyl-C(=O)O-heterocycle, C_{1-4} alkyl-C(=O)O-heteroaryl, or C_{1-4} alkoxy; and

R^9 is O or S;

optionally in a pharmaceutically acceptable carrier or diluent;

in the manufacture of a medicament for the treatment of a coronavirus, togavirus or picornavirus infection in a host.

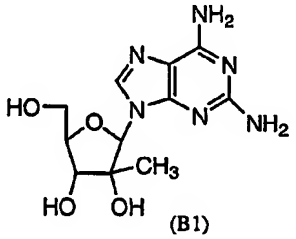
75. The use of claim 74 wherein the compound of Formula (AA) has the structure of (A1):



(A1)

or a pharmaceutically acceptable salt or prodrug thereof.

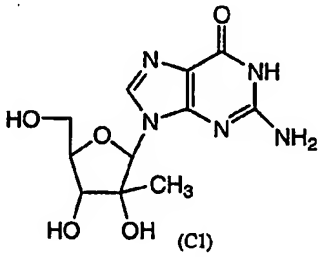
76. The use of claim 74 wherein the compound of Formula (AA) has the structure of (B1):



(B1)

or a pharmaceutically acceptable salt or prodrug thereof.

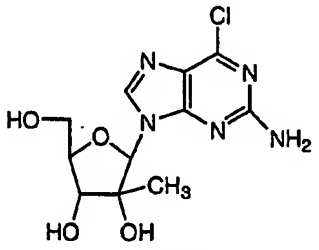
77. The use of claim 74 wherein the compound of Formula (AA) has the structure of (C1):



(C1)

or a pharmaceutically acceptable salt or prodrug thereof.

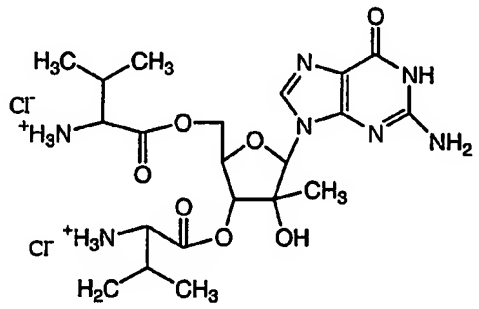
78. The use of claim 74 wherein the compound of Formula (AA) has the structure of (D1):



(D1)

or a pharmaceutically acceptable salt or prodrug thereof.

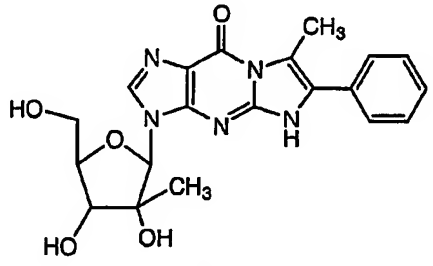
79. The use of claim 74 wherein the compound of Formula (AA) has the structure of (E1):



(E1)

or a pharmaceutically acceptable salt or prodrug thereof.

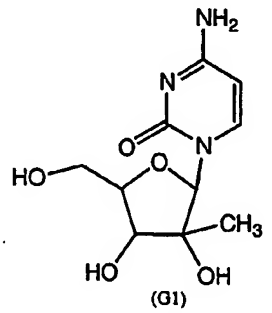
80. The use of claim 74 wherein the compound of Formula (AA) has the structure of (F1):



(F1)

or a pharmaceutically acceptable salt or prodrug thereof.

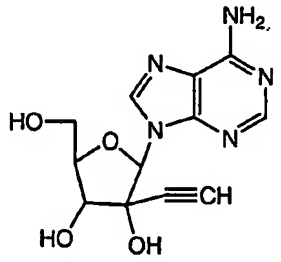
81. The use of claim 74 wherein the compound of Formula (AA) has the structure of (G1):



(G1)

or a pharmaceutically acceptable salt or prodrug thereof.

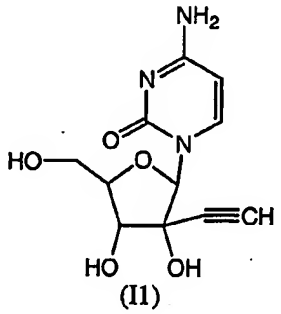
82. The use of claim 74 wherein the compound of Formula (AA) has the structure of (H1):



(H1)

or a pharmaceutically acceptable salt or prodrug thereof.

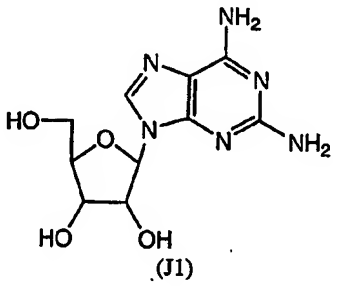
83. The use of claim 74 wherein the compound of Formula (AA) has the structure of (I1):



(I1)

or a pharmaceutically acceptable salt or prodrug thereof.

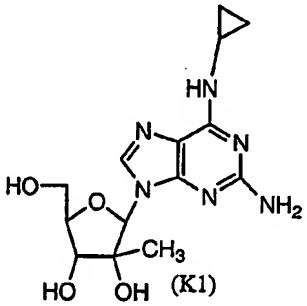
84. The use of claim 74 wherein the compound of Formula (AA) has the structure of (J1):



(J1)

or a pharmaceutically acceptable salt or prodrug thereof.

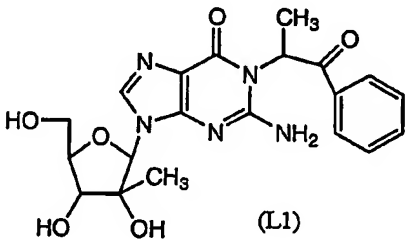
85. The use of claim 74 wherein the compound of Formula (AA) has the structure of (K1):



(K1)

or a pharmaceutically acceptable salt or prodrug thereof.

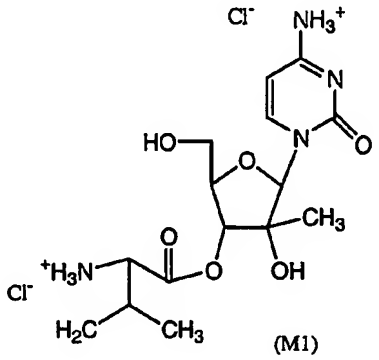
86. The use of claim 74 wherein the compound of Formula (AA) has the structure of (L1):



(L1)

or a pharmaceutically acceptable salt or prodrug thereof.

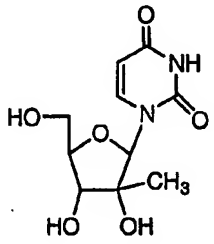
87. The use of claim 74 wherein the compound of Formula (AA) has the structure of (M1):



(M1)

or a pharmaceutically acceptable salt or prodrug thereof.

88. The use of claim 74 wherein the compound of Formula (AA) has the structure of (N1):



(N1)

or a pharmaceutically acceptable salt or prodrug thereof.

89. The use of claim any one of claims 74-88, further in combination and/or alternation with one or more other anti-viral agent.

90. The use of claim 89, wherein the other anti-viral agent is an anti-coronavirus, anti-togavirus, and/or anti-picornavirus agent.

91. The use of claim 90, wherein the anti-coronavirus agent is an anti-SARS-CoV agent.

92. The use of claim 90, wherein the anti-togavirus agent is an anti-rubivirus or an anti-alphavirus agent.

93. The use of claim 90, wherein the anti-picornavirus is an anti-enterovirus, anti-rhinovirus, anti-cardiovirus and/or anti-aphthovirus agent.

94. The use of claim 93, wherein the anti-enterovirus agent is an anti-Coxsackievirus, anti-poliovirus, anti-hepatitis A virus, and/or an anti-echovirus agent.

95. The use of any one of claims 74-94, wherein the coronavirus is a SARS-CoV virus.

96. The use of any one of claims 74-94, wherein the togavirus is a rubivirus (the causative agent for rubella) or an alphavirus (the causative agent for encephalitis)

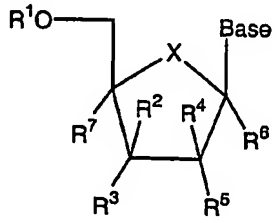
97. The use of any one of claims 74-94, wherein the a picornavirus is an enterovirus, a rhinovirus, a cardiovirus or an aphthovirus.

98. The use of claim 97, wherein the enterovirus is a Coxsackievirus, poliovirus, hepatitis A virus, echovirus, or a human enterovirus species.

99. The use of any one of claims 74-98 wherein the host is a mammal.

100. The use of claim 99 wherein the mammal is a human.

101. A pharmaceutical composition for the treatment of a coronavirus, togavirus or picornavirus infection in a host, comprising an effective amount of a compound of the Formula (AA):



AA

or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein:

R^1 is H; phosphate; mono-, di-, or triphosphate; stabilized phosphate prodrug; optionally substituted acyl; optionally substituted lower acyl; optionally substituted alkyl; optionally substituted lower alkyl; sulfonate ester; alkyl or arylalkyl sulfonyl; methanesulfonyl; aryl; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; optionally substituted

arylsulfonyl; a lipid; a phospholipid; an amino acid derivative; a carbohydrate; a peptide; cholesterol; or other pharmaceutically acceptable leaving group that when administered *in vivo*, provides a compound wherein R^1 is independently H or phosphate;

each R^2 and R^4 independently is H, OH, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, halo (F, Cl, Br, I), NO_2, NH_2, N_3, CH_2N_3, CH_2NH_2, CN, CH_2CN, CH_2N_3, CH_2NHCH_3, $CH_2N(CH_3)_2$, CH_2OH, halogenated alkyl, alkoxy, CF_3, $C(A)_3$, 2-Br-ethyl, CH_2F, CH_2Cl, CH_2CF_3, CF_2CF_3, $CH_2(A)$, $C(A)_2(A)_3$, SCN, OCN, NCO, haloalkenyl, Br-vinyl, haloalkynyl; $-(CH_2)_mC(O)OR^{13}$, $-(CH_2)_mC(O)SR^{13}$; -O(alkenyl), $-(CH_2)_mNHR^{13}$, $-(CH_2)_mN(R^{13})_2$, $-(CH_2)_mC(O)NHR^{13}$, $-(CH_2)_mC(O)N(R^{13})_2$, $-C(O)OR^{13}$, $-O(R^{13})$, an optionally substituted carbocycle, an optionally substituted heterocycle, an optionally substituted heteroaryl, or C_{3-7} cycloalkylamino;

each R^3, R^5 and R^6 independently is H, OH, an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, halo (F, Cl, Br, or I), NO_2, NH_2, N_3, CH_2N_3, CH_2NH_2, CN, CH_2CN, CH_2N_3, CH_2NHCH_3, $CH_2N(CH_3)_2$, CH_2OH, halogenated alkyl, alkoxy, CF_3, $C(A)_3$, 2-Br-ethyl, CH_2F, CH_2Cl, CH_2CF_3, CF_2CF_3, $CH_2(A)$, $C(A)_2(A)_3$, SCN, OCN, NCO, haloalkenyl, Br-vinyl, haloalkynyl; $-(CH_2)_mC(O)OR^{13}$, $-(CH_2)_mC(O)SR^{13}$; -O(alkenyl), $-(CH_2)_mNHR^{13}$, $-(CH_2)_mN(R^{13})_2$, $-(CH_2)_mC(O)NHR^{13}$, $-(CH_2)_mC(O)N(R^{13})_2$, $-C(O)OR^{13}$, $-O(R^{13})$, an optionally substituted 3-7 membered carbocyclic ring, a C_{3-7} cycloalkylamino, an optionally substituted heterocycle, an optionally substituted heteroaryl, a C_{3-7} cycloalkylamino, CF_3, mercapto, optionally substituted C_{1-4} alkyl, C_{1-12} alkoxy, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{2-6} alkenyloxy, C_{1-4} alkylthio, C_{1-8} alkylcarbonyloxy, aryloxycarbonyl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, Br-vinyl, -C(O)O(alkyl), O-phosphate, O-mono-, di-, or triphosphate, O-stabilized phosphate prodrug; O-acyl; O-lower acyl; O-alkyl; O-lower alkyl; O-sulfonate ester, O-alkyl or O-arylalkyl sulfonyl; O-methanesulfonyl; O-benzyl, wherein the phenyl group is optionally substituted with one or more substituents; -OC(O)O-aryl; -OC(O)O-aralkyl; -S(acyl); -S(alkyl); -

S(alkenyl); optionally substituted O-arylsulfonyl; an O-linked lipid, including an O-phospholipid; an O-linked amino acid; an O-linked carbohydrate; an O-linked peptide; O-linked cholesterol; or other O-linked pharmaceutically acceptable leaving group that when administered *in vivo*, provides independently OH or O-phosphate;

each R^7 is independently H, $-OR^1$, -OH, $-NO_2$, $-CF_3$, $-NH_2$, Cl, F, Br, I, N_3, CN, optionally substituted alkyl, optionally substituted alkenyl or alkynyl, Br-vinyl, $-CH_2OH$, -O(R), alkoxy, $-(CH_2)_mC(O)O(R)$, -OC(O)O-aryl, -OC(O)O-aralkyl, -SR, $-(CH_2)_mNHR$, $-(CH_2)_mN(R)_2$, or C_{3-7} cycloalkylamino;

each R is H, alkyl, alkenyl, alkynyl, acyl, aryl or aralkyl;

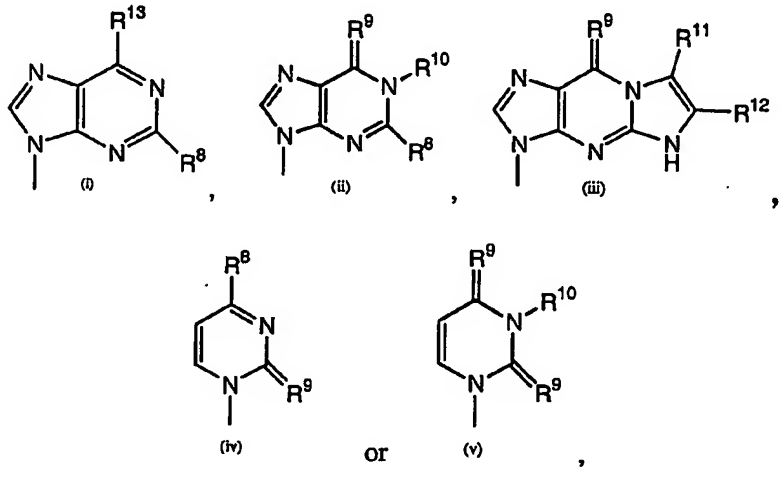
X is O, S, SO_2, CH_2, or CHOH;

m is 0, 1 or 2;

R^{13} is H, alkyl, alkenyl, alkynyl, acyl, aryl or aralkyl;

A is H, OH, C_{1-4} alkyl, halo (F, Cl, Br, or I), azido, cyano, C_{2-6} alkenyl, C_{2-6} alkynyl, Br-vinyl, 2-Br-ethyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), CF_3, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), $-N(\text{lower alkyl})_2$, or $-N(acyl)_2$; and

Base is a purine, a pyrimidine or a base selected from the group consisting of:



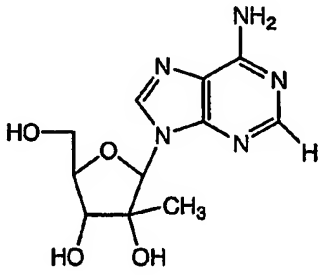
wherein:

each R^8, R^{10}, R^{11}, R^{12} and R^{13} independently is H, NH_2, SH, CF_3, halo, NO_2, N_3, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted phenyl, -NH-cycloalkyl, -NH-cycloalkenyl, -NH-heterocycle, -NH-heteroaryl, -O-cycloalkyl, -O-cycloalkenyl, -O-heterocycle, -O-heteroaryl, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{3-6} cycloalkylamino, C_{1-4} alkyl-C(=O)OH, C_{1-4} alkyl-C(=O)O-aryl, C_{1-4} alkyl-C(=O)O-phenyl), C_{1-4} alkyl-C(=O)O-heterocycle, C_{1-4} alkyl-C(=O)O-heteroaryl, or C_{1-4} alkoxy; and

R^9 is O or S;

optionally in a pharmaceutically acceptable carrier or diluent.

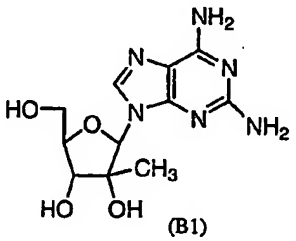
102. The pharmaceutical composition of claim 101 wherein the compound of Formula (AA) has the structure of (A1):



(A1)

or a pharmaceutically acceptable salt or prodrug thereof.

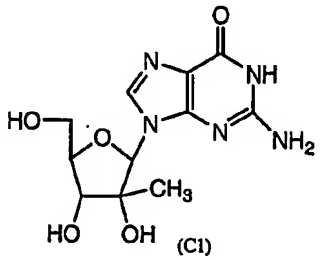
103. The pharmaceutical composition of claim 101 wherein the compound of Formula (AA) has the structure of (B1):



(B1)

or a pharmaceutically acceptable salt or prodrug thereof.

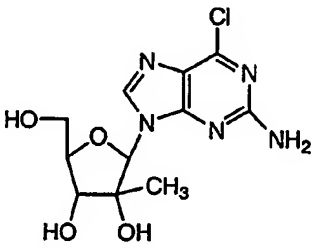
104. The pharmaceutical composition of claim 101 wherein the compound of Formula (AA) has the structure of (C1):



(C1)

or a pharmaceutically acceptable salt or prodrug thereof.

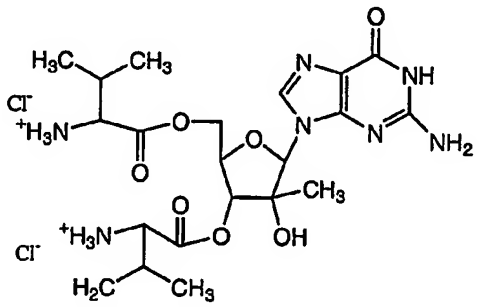
105. The pharmaceutical composition of claim 101 wherein the compound of Formula (AA) has the structure of (D1):



(D1)

or a pharmaceutically acceptable salt or prodrug thereof.

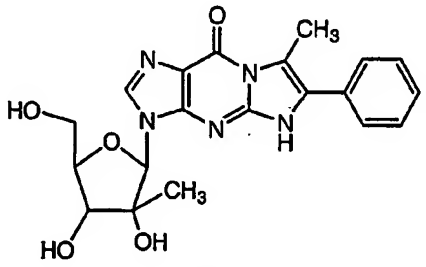
106. The pharmaceutical composition of claim 101 wherein the compound of Formula (AA) has the structure of (E1):



(E1)

or a pharmaceutically acceptable salt or prodrug thereof.

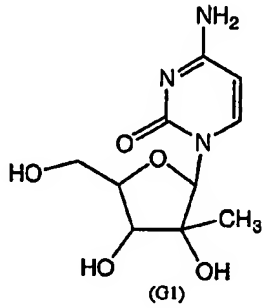
107. The pharmaceutical composition of claim 101 wherein the compound of Formula (AA) has the structure of (F1):



(F1)

or a pharmaceutically acceptable salt or prodrug thereof.

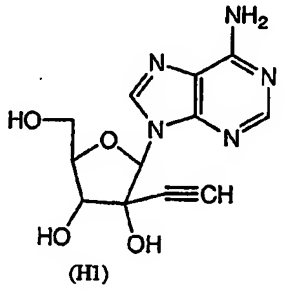
108. The pharmaceutical composition of claim 101 wherein the compound of Formula (AA) has the structure of (G1):



(G1)

or a pharmaceutically acceptable salt or prodrug thereof.

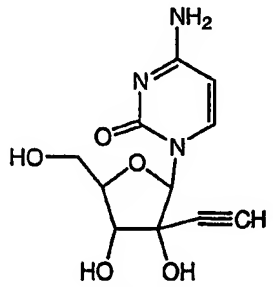
109. The pharmaceutical composition of claim 101 wherein the compound of Formula (AA) has the structure of (H1):



(H1)

or a pharmaceutically acceptable salt or prodrug thereof.

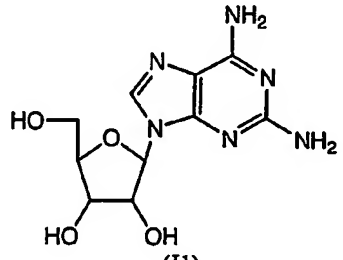
110. The pharmaceutical composition of claim 101 wherein the compound of Formula (AA) has the structure of (I1):



(I1)

or a pharmaceutically acceptable salt or prodrug thereof.

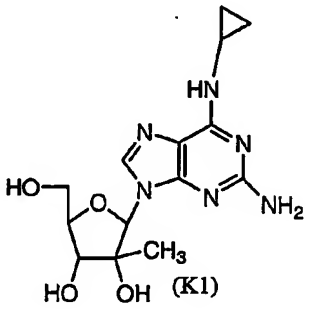
111. The pharmaceutical composition of claim 101 wherein the compound of Formula (AA) has the structure of (J1):



(J1)

or a pharmaceutically acceptable salt or prodrug thereof.

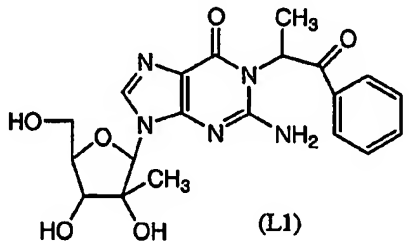
112. The pharmaceutical composition of claim 101 wherein the compound of Formula (AA) has the structure of (K1):



(K1)

or a pharmaceutically acceptable salt or prodrug thereof.

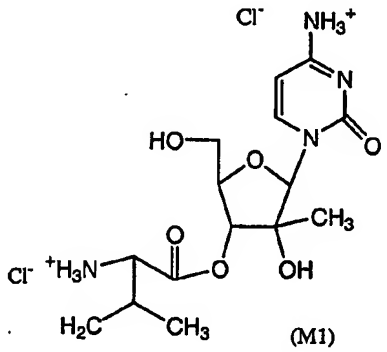
113. The pharmaceutical composition of claim 101 wherein the compound of Formula (AA) has the structure of (L1):



(L1)

or a pharmaceutically acceptable salt or prodrug thereof.

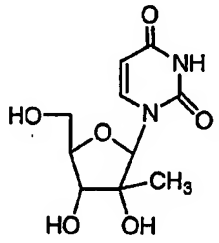
114. The pharmaceutical composition of claim 101 wherein the compound of Formula (AA) has the structure of (M1):



(M1)

or a pharmaceutically acceptable salt or prodrug thereof.

115. The pharmaceutical composition of claim 101 wherein the compound of Formula (AA) has the structure of (N1):



(N1)

or a pharmaceutically acceptable salt or prodrug thereof.

116. The pharmaceutical composition of any one of claims claim 101-115, further in combination and/or alternation with one or more other anti-viral agent.

117. The pharmaceutical composition of claim 116, wherein the other anti-viral agent is an anti-coronavirus, anti-togavirus, and/or anti-picornavirus agent.

118. The pharmaceutical composition of claim 117, wherein the anti-coronavirus agent is an anti-SARS-CoV agent.

119. The pharmaceutical composition of claim 117, wherein the anti-togavirus agent is an anti-rubivirus or an anti-alphavirus agent.

120. The pharmaceutical composition of claim 117, wherein the anti-picornavirus is an anti-enterovirus, anti-rhinovirus, anti-cardiovirus and/or anti-aphthovirus agent.

121. The pharmaceutical composition of claim 120, wherein the anti-enterovirus agent is an anti-Coxsackievirus, anti-poliovirus, anti-hepatitis A virus, and/or an anti-echovirus agent.

122. The pharmaceutical composition of any one of claims 101-121, wherein the coronavirus infection is a SARS-CoV infection.

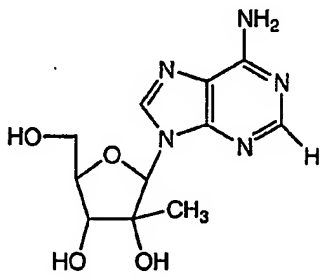
123. The pharmaceutical composition of any one of claims 101-121, wherein the togavirus infection is a rubivirus infection (the causative agent for rubella) or an alphavirus infection (the causative agent for encephalitis).

124. The pharmaceutical composition of any one of claims 101-121, wherein the a picornavirus infection is an enterovirus, a rhinovirus, a cardiovirus or an aphthovirus infection.

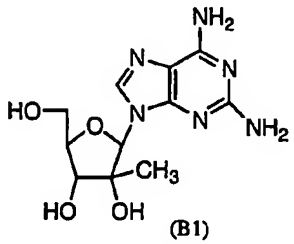
125. The pharmaceutical composition of claim 124, wherein the enterovirus is a Coxsackievirus, poliovirus, hepatitis A virus, echovirus, or a human enterovirus species.

126. The pharmaceutical composition of any one of claims 101-125, wherein the host is a mammal.

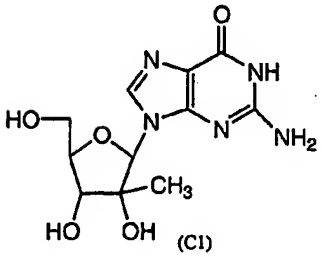
127. The pharmaceutical composition of claim 126 wherein the mammal is a human.



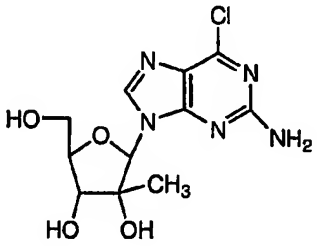
(A1)



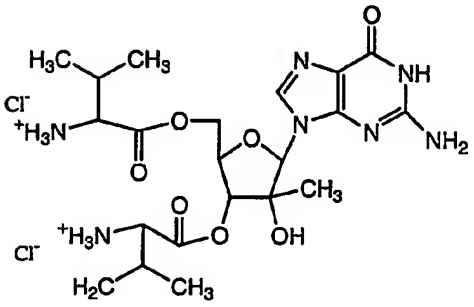
(B1)



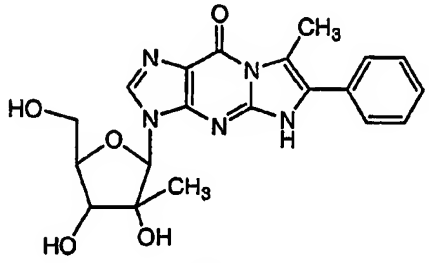
(C1)



(D1)

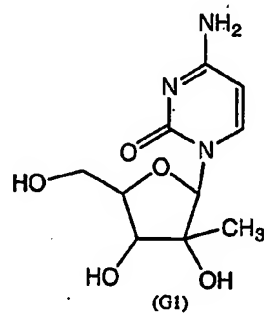


(E1)

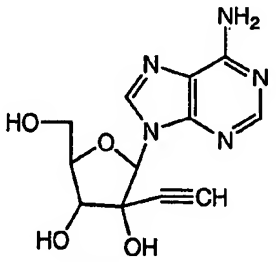


(F1)

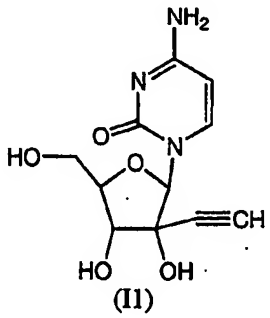
Figure 1



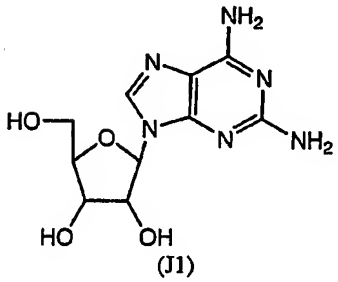
(G1)



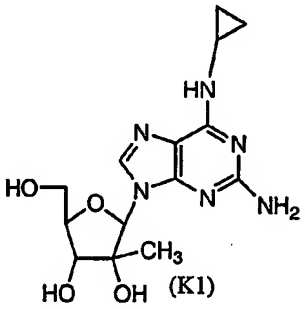
(H1)



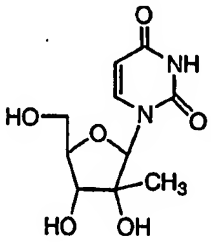
(I1)



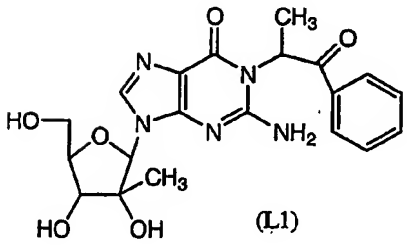
(J1)



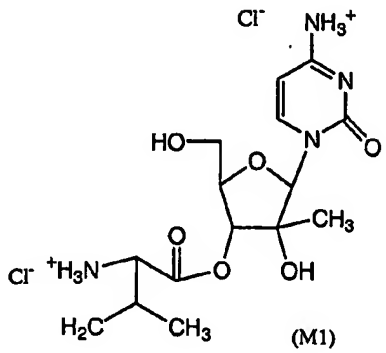
(K1)



(N1)

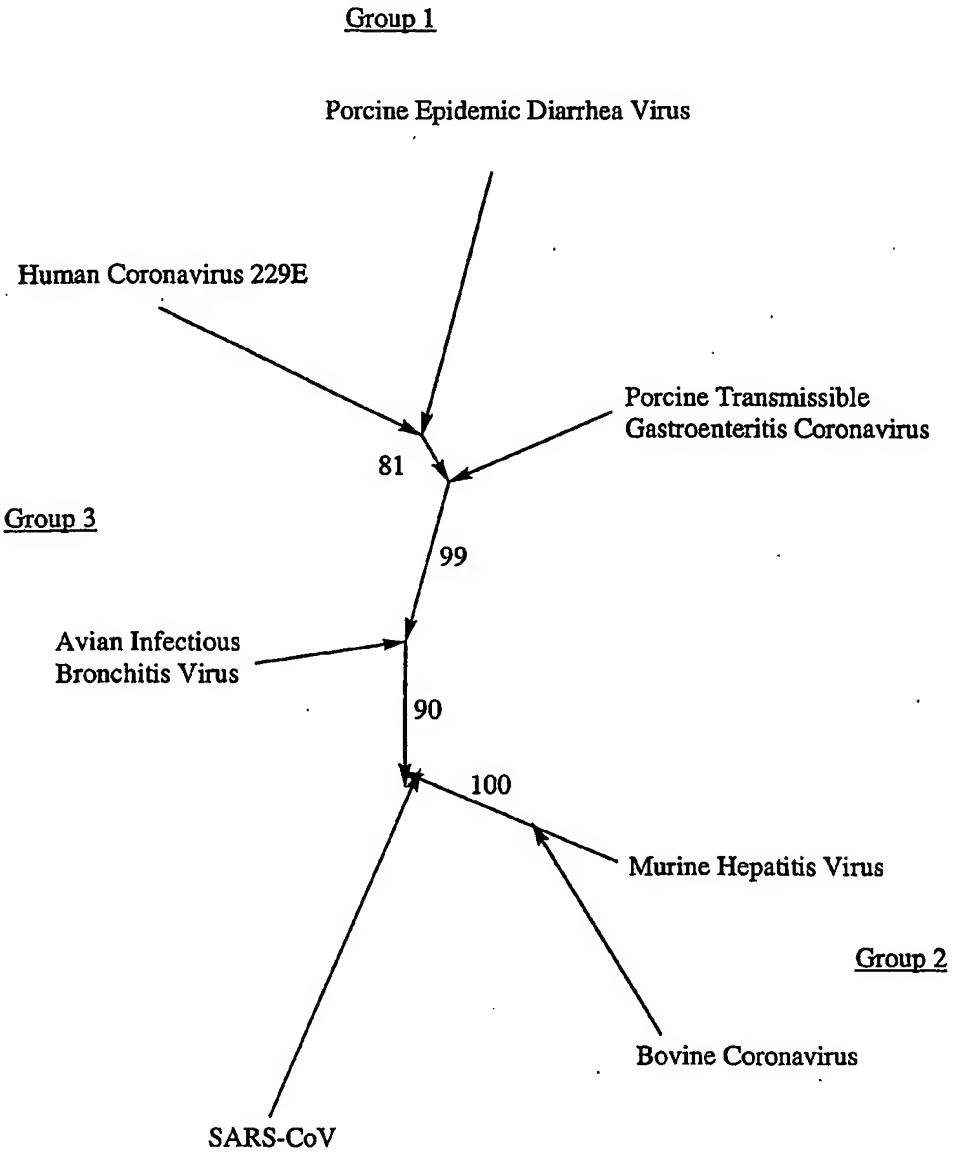


(L1)



(M1)

Figure 1 (Continued)



Adapted from: S. Gunther, Dept. of Virology, Bernhard Nocht Institute for Tropical Medicine; http://SARSReference.com/archive/phylogenetictree.jpg

Figure 2